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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 498/00 | A2

(11) International Publication Number: WO 99/02532

(43) International Publication Date: 21 January 1999 (21.01.99)

(21) International Application Number: PCT/EP98/04141

(22) International Filing Date: 3 July 1998 (03.07.98)

(30) Priority Data:

1646/97	7 July 1997 (07.07.97)	CH
2145/97	11 September 1997 (11.09.97)	CH

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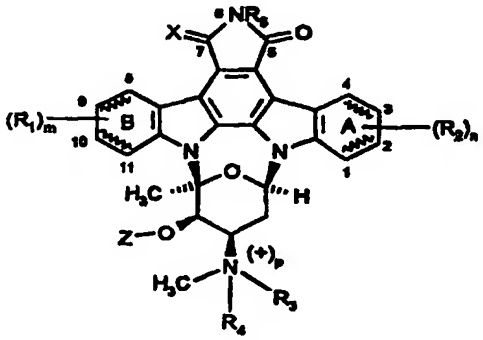
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

Without international search report and to be republished upon receipt of that report.

(54) Title: PARTIALLY HYDROGENATED POLYCYCLIC COMPOUNDS



(I)

(57) Abstract

The invention relates to a compound of formula (I), wherein R_1, R_2, R_3, R_4, R_5, n, m, p, X and Z are as defined in the description; and either the two bonds characterised by wavy lines are absent in ring A and replaced by a total of 4 hydrogen atoms, and the two wavy lines in ring B each, together with the respective parallel bond, signify a double bond; or the two bonds characterised by wavy lines are absent in ring B and replaced by a total of 4 hydrogen atoms, and the two wavy lines in ring A each, together with the respective parallel bond, signify a double bond; or both in ring A and in ring B all of the 4 wavy bonds are absent and are replaced by a total of 8 hydrogen atoms; or a salt thereof, if at least one salt–forming group is present. These have, for example, an antitumour effect.

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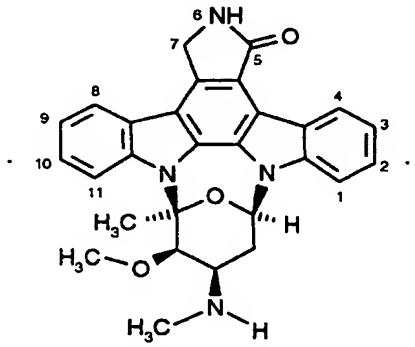
Partially hydrogenated polycyclic compounds

Nature of the invention

The invention relates to unsubstituted or N-mono- or N,N-disubstituted tetra- and octahydro-staurosporine derivatives, namely unsubstituted or N-mono- or N,N-disubstituted 1,2,3,4-tetrahydro-, 8,9,10,11-tetrahydro-, or 1,2,3,4,8,9,10,11-octahydro-staurosporine derivatives, to processes for their preparation, to pharmaceutical preparations containing these compounds, and to methods of treatment with these compounds, and to their use as pharmacological agents or for the preparation of a pharmacological agent.

Background to the invention

Staurosporine of formula II



(II),

as raw material for the derivatives of the invention, was first isolated in 1977 from cultures of *Streptomyces staurosporeus*, AWAYA, TAKAHASHI and OMURA, sp. nov. AM 2282, (see S. Omura et al., J. Antibiot. 30, 275-281 (1977)). The absolute configuration was first published by N. Funato et al. (see Tetrahedron Letters 35:8, 1251-1254 (1994)) and corresponds to the mirror image of the structure that was used previously in the literature to indicate the relative configuration of staurosporine. At least it indicates the relative configuration correctly.

Staurosporine exerts a marked inhibitory action on protein kinase C, but it also markedly inhibits other protein kinases and therefore does not have the selectivity that would be necessary for therapeutic use. Although greater selectivity is shown by staurosporine

derivatives substituted by customary acyl radicals, such as benzoyl, these N-acylated staurosporine derivatives are as a rule rather poorly soluble in water and therefore do not readily lend themselves to formulation as suitable pharmaceutical dosage forms.

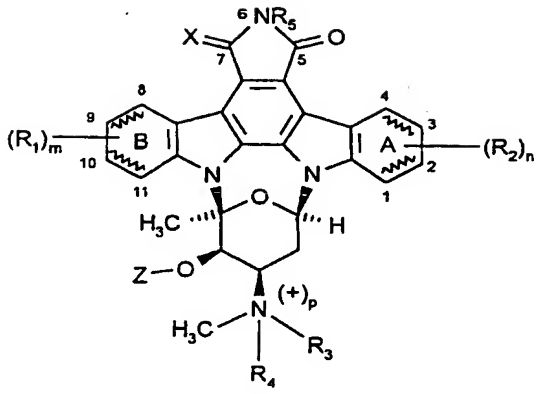
The aim of the present invention is to prepare a completely new class of staurosporine derivatives which retain the advantage of a high degree of efficacy in the inhibition of serine / threonine kinases, such as protein kinase C in particular, especially protein kinase C-α, and also some tyrosine kinases, such as PDGF-R and VEGF-R in particular (PDGF stands for "Platelet Derived Growth Factor", VEGF for "Vascular Endothelial Growth Factor"), and versus other protein kinases, mostly of a selective nature, especially versus EGF receptor-tyrosine kinase (EGF stands for "Epidermal Growth Factor"). In addition, it is intended that the staurosporine derivatives to be prepared should be highly effective when given orally and show such good solubility that they can be formulated as suitable pharmaceutical dosage forms without any major complications. A high degree of efficacy is very important for inhibiting the growth of proliferative cells.

Summary of the invention

Surprisingly, it has been found that, when hydrogenating staurosporine, partial hydrogenation is possible. This leads to a completely new class of staurosporine derivatives, wherein the compounds of the invention have advantageous pharmacological properties, and especially meet all or at least several of the above objectives. In addition, they show an excellent inhibitory effect on the growth of tumour cells.

Full description of the invention

The invention relates in particular to a compound of formula I,



(I)

wherein R_1 and R_2 are, independently of one another, unsubstituted or substituted alkyl, halogen, hydroxy, etherified or esterified hydroxy, amino, mono- or disubstituted amino, cyano, nitro, mercapto, substituted mercapto, carboxy, esterified carboxy, carbamoyl, N-mono- or N,N-di-substituted carbamoyl, sulfo, substituted sulfonyl, aminosulfonyl or N-mono- or N,N-di-substituted aminosulfonyl;

n and m are, independently of one another, a number from and including 0 to and including 4;

R_3 and R_4 are, independently of one another, hydrogen, an aliphatic, carbocyclic, or carbocyclic-aliphatic radical with up to 29 carbon atoms in each case, a heterocyclic or heterocyclic-aliphatic radical with up to 20 carbon atoms in each case, and in each case up to 9 heteroatoms, wherein R_4 may also be absent;

or R_3 is acyl with up to 30 carbon atoms and R_4 is absent;

p is 0 if R_4 is absent, or is 1 if R_3 and R_4 are both present and in each case are one of the aforementioned radicals;

R_5 is hydrogen, an aliphatic, carbocyclic, or carbocyclic-aliphatic radical with up to 29 carbon atoms in each case, or a heterocyclic or heterocyclic-aliphatic radical with up to 20 carbon atoms in each case, and in each case up to 9 heteroatoms, or acyl with up to 30 carbon atoms;

X stands for 2 hydrogen atoms; for 1 hydrogen atom and hydroxy; for O; or for hydrogen and lower alkoxy;

Z stands for hydrogen or lower alkyl;

and either the two bonds characterised by wavy lines are absent in ring A and replaced by 4 hydrogen atoms, and the two wavy lines in ring B each, together with the respective parallel bond, signify a double bond;

or the two bonds characterised by wavy lines are absent in ring B and replaced by a total of 4 hydrogen atoms, and the two wavy lines in ring A each, together with the respective parallel bond, signify a double bond;

or both in ring A and in ring B all of the 4 wavy bonds are absent and are replaced by a total of 8 hydrogen atoms;

or a salt thereof, if at least one salt-forming group is present.

The general terms and definitions used preferably have hereinbefore and hereinafter the following meanings:

The prefix "lower" indicates that the associated radical preferably has up to and including a maximum of 7 carbon atoms, especially up to and including a maximum of 4 carbon atoms.

Lower alkyl is especially methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, or tert-butyl, and also pentyl, hexyl, or heptyl.

Unsubstituted or substituted alkyl is preferably C_1-C_{20}alkyl, especially lower alkyl, typically methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, or tert-butyl, which is unsubstituted or substituted especially by halogen, such as fluorine, chlorine, bromine, or iodine, C_6-C_{14}aryl, such as phenyl or naphthyl, hydroxy, etherified hydroxy, such as lower alkoxy, phenyl-lower alkoxy or phenyloxy, esterified hydroxy, such as lower alkanoyloxy or

benzoyloxy, amino, mono- or disubstituted amino, such as lower alkylamino, lower alkanoylamino, phenyl-lower alkylamino, N,N-di-lower alkylamino, N,N-di-(phenyl-lower alkyl)amino, cyano, mercapto, substituted mercapto, such as lower alkylthio, carboxy, esterified carboxy, such as lower alkoxycarbonyl, carbamoyl, N-mono- or N,N-disubstituted carbamoyl, such as N-lower alkylcarbamoyl or N,N-di-lower alkylcarbamoyl, sulfo, substituted sulfo, such as lower alkanesulfonyl or lower alkoxysulfonyl, aminosulfonyl or N-mono- or N,N-disubstituted aminosulfonyl, such as N-lower alkylaminosulfonyl or N,N-di-lower alkylaminosulfonyl.

Halogen is preferably fluorine, chlorine, bromine, or iodine, especially fluorine or chlorine.

Etherified hydroxy is especially lower alkoxy, C_6-C_{14}aryloxy, such as phenyloxy, or C_6-C_{14}aryl-lower alkoxy, such as benzyloxy.

Esterified hydroxy is preferably lower alkanoyloxy or C_6-C_{14}arylcarbonyloxy, such as benzoyloxy.

Mono- or disubstituted amino is especially amino monosubstituted or disubstituted by lower alkyl, C_6-C_{14}aryl, C_6-C_{14}aryl-lower alkyl, lower alkanoyl, or C_6-C_{12}arylcarbonyl.

Substituted mercapto is especially lower alkylthio, C_6-C_{14}arylthio, C_6-C_{14}aryl-lower alkylthio, lower alkanoylthio, or C_6-C_{14}aryl-lower alkanoylthio.

Esterified carboxy is especially lower alkoxycarbonyl, C_6-C_{14}aryl-lower alkoxycarbonyl or C_6-C_{14}aryloxycarbonyl.

N-Mono- or N,N-disubstituted carbamoyl is especially carbamoyl N-monosubstituted or N,N-disubstituted by lower alkyl, C_6-C_{14}aryl or C_6-C_{14}aryl-lower alkyl.

Substituted sulfonyl is especially C_6-C_{14}arylsulfonyl, such as toluenesulfonyl, C_6-C_{14}aryl-lower alkanesulfonyl or lower alkanesulfonyl.

N-Mono- or N,N-disubstituted aminosulfonyl is especially aminosulfonyl N-monosubstituted or N,N-disubstituted by lower alkyl, C_5-C_{14}aryl or C_6-C_{14}aryl-lower alkyl.

C_6-C_{14}Aryl is an aryl radical with 6 to 14 carbon atoms in the ring system, such as phenyl, naphthyl, fluorenyl, or indenyl, which is unsubstituted or is substituted especially by halogen, such as fluorine, chlorine, bromine, or iodine, phenyl or naphthyl, hydroxy, lower alkoxy, phenyl-lower alkoxy, phenyloxy, lower alkanoyloxy, benzoyloxy, amino, lower alkylamino, lower alkanoylamino, phenyl-lower alkylamino, N,N-di-lower alkylamino, N,N-di-(phenyl-lower alkyl)amino, cyano, mercapto, lower alkylthio, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, sulfo, lower alkanesulfonyl, lower alkoxysulfonyl, aminosulfonyl, N-lower alkylaminosulfonyl, or N,N-di-lower alkylaminosulfonyl.

The indices n and m are in each case preferably 1 or especially 0. In general, compounds of formula I in which n and m are in each case 0 (zero) are especially preferred.

An aliphatic carbohydrate radical with up to 29 carbon atoms R_3 or R_4, which is substituted by acyclic substituents and preferably has a maximum of 18, especially a maximum of 12, and as a rule not more than 7 carbon atoms, may be saturated or unsaturated and is especially an unsubstituted or a straight-chain or branched lower alkyl, lower alkenyl, lower alkadienyl, or lower alkinyl radical substituted by acyclic substituents. Lower alkyl is, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl or tert-butyl, and also n-pentyl, isopentyl, n-hexyl, isohexyl and n-heptyl; lower alkenyl is, for example, allyl, propenyl, isopropenyl, 2- or 3-methallyl and 2- or 3-butenyl; lower alkadienyl is, for example, 1-penta-2,4-dienyl; lower alkinyl is, for example, propargyl or 2-butinyl. In corresponding unsaturated radicals, the double bond is especially located in a position higher than the α-position in relation to the free valency. Substituents are especially the acyl radicals defined hereinbelow as substituents of R°, preferably free or esterified carboxy, such as carboxy or lower alkoxycarbonyl, cyano or di-lower alkylamino.

A carbocyclic or carbocyclic-aliphatic radical R_3 or R_4 with up to 29 carbon atoms in each case is especially an aromatic, a cycloaliphatic, a cycloaliphatic-aliphatic, or an aromatic-aliphatic radical which is either present in unsubstituted form or substituted by radicals

referred to hereinbelow as substituents of R°. An aromatic radical (aryl radical) R_3 or R_4 is most especially a phenyl, also a naphthyl, such as 1- or 2-naphthyl, a biphenylyl, such as especially 4-biphenylyl, and also an anthryl, fluorenyl and azulenyl, as well as their aromatic analogues with one or more saturated rings, which is either present in unsubstituted form or substituted by radicals referred to hereinbelow as substituents of R°. Preferred aromatic-aliphatic radicals are aryl-lower alkyl- and aryl-lower alkenyl radicals, e.g. phenyl-lower alkyl or phenyl-lower alkenyl with a terminal phenyl radical, such as for example benzyl, phenethyl, 1-, 2-, or 3-phenylpropyl, diphenylmethyl (benzhydryl), trityl, and cinnamyl, and also 1- or 2-naphthylmethyl. Of aryl radicals carrying acyclic radicals, such as lower alkyl, special mention is made of o-, m- and p-tolyl and xylyl radicals with variously situated methyl radicals.

A cycloaliphatic radical R_3 or R_4 with up to 29 carbon atoms is especially a substituted or preferably unsubstituted mono-, bi-, or polycyclic cycloalkyl-, cycloalkenyl-, or cycloalkadienyl radical. Preference is for radicals with a maximum of 14, especially 12, ring-carbon atoms and 3- to 8-, preferably 5- to 7-, and most especially 6-member rings which can also carry one or more, for example two, aliphatic hydrocarbon radicals, for example those named above, especially the lower alkyl radicals, or other cycloaliphatic radicals. Preferred substituents are the acyclic substituents named hereinbelow for R°.

A cycloaliphatic-aliphatic radical R_3 or R_4 with up to 29 carbon atoms is a radical in which an acyclic radical, especially one with a maximum of 7, preferably a maximum of 4 carbon atoms, such as especially methyl, ethyl, and vinyl, carries one or more cycloaliphatic radicals as defined hereinabove. Special mention is made of cycloalkyl-lower alkyl radicals, as well as their analogues which are unsaturated in the ring and/or in the chain, but are non-aromatic, and which carry the ring at the terminal carbon atom of the chain. Preferred substituents are the acyclic substituents named hereinbelow for R°.

Heterocyclic radicals R_3 or R_4 with up to 20 carbon atoms each and up to 9 heteroatoms each are especially monocyclic, but also bi- or polycyclic, aza-, thia-, oxa-, thiaza-, oxaza-, diaza-, triaza-, or tetrazacyclic radicals of an aromatic character, as well as corresponding heterocyclic radicals of this type which are partly or most especially wholly saturated, these radicals – if need be – possibly carrying further acyclic, carbocyclic, or heterocyclic radicals

and/or possibly mono-, di-, or polysubstituted by functional groups, preferably those named hereinabove as substituents of aliphatic hydrocarbon radicals. Most especially they are unsubstituted or substituted monocyclic radicals with a nitrogen, oxygen, or sulfur atom, such as 2-aziridinyl, and especially aromatic radicals of this type, such as pyrryl, for example 2-pyrryl or 3-pyrryl, pyridyl, for example 2-, 3-, or 4-pyridyl, and also thienyl, for example 2- or 3-thienyl, or furyl, for example 2-furyl; analogous bicyclic radicals with an oxygen, sulfur, or nitrogen atom are, for example, indolyl, typically 2- or 3-indolyl, quinolyl, typically 2- or 4-quinolyl, isoquinolyl, typically 3- or 5-isoquinolyl, benzofuranyl, typically 2-benzofuranyl, chromenyl, typically 3-chromenyl, or benzothienyl, typically 2- or 3-benzothienyl; preferred monocyclic and bicyclic radicals with several heteroatoms are, for example, imidazolyl, typically 2- or 4-imidazolyl, pyrimidinyl, typically 2-or 4-pyrimidinyl, oxazolyl, typically 2-oxazolyl, isoxazolyl, typically 3-isoxazolyl, or thiazolyl, typically 2-thiazolyl, and benzimidazolyl, typically 2-benzimidazolyl, benzoxazolyl, typically 2-benzoxazolyl, or quinazolyl, typically 2-quinazolinyl. Appropriate partially or, especially, completely saturated analogous radicals may also be considered, such as 2-tetrahydrofuryl, 2- or 3-pyrrolidinyl, 2-, 3-, or 4-piperidyl, and also 2-or 3-morpholinyl, 2- or 3-thiomorpholinyl, 2-piperazinyl and N-mono- or N,N'-bis-lower alkyl-2-piperazinyl radicals. These radicals may also carry one or more acyclic, carbocyclic, or heterocyclic radicals, especially those mentioned hereinabove. The free valency of the heterocyclic radicals R_3 or R_4 must emanate from one of their carbon atoms. Heterocyclyl may be unsubstituted or substituted by one or more, preferably one or two, of the substituents named hereinbelow for R°.

Heterocyclic-aliphatic radicals R_3 or R_4 especially lower alkyl radicals, especially with a maximum of 7, preferably a maximum of 4 carbon atoms, for example those named hereinabove, which carry one, two, or more heterocyclic radicals, for example those named in the preceding paragraph, the heterocyclic ring possibly being linked to the aliphatic chain also by one of its nitrogen atoms. A preferred heterocyclic-aliphatic radical R_1 is, for example, imidazol-1-ylmethyl, 4-methylpiperazin-1-ylmethyl, piperazin-1-ylmethyl, 2-(morpholin-4-yl)ethyl and also pyrid-3-ylmethyl. Heterocyclyl may be unsubstituted or substituted by one or more, preferably one or two, of the substituents named hereinbelow for R°.

A heteroaliphatic radical R_3 or R_4 with up to 20 carbon atoms each and up to 10 heteroatoms each is an aliphatic radical which, instead of one, two, or more carbon atoms, contains identical or different heteroatoms, such as especially oxygen, sulfur, and nitrogen. An especially preferred arrangement of a heteroaliphatic radical R_1 takes the form of oxa-alkyl radicals in which one or more carbon atoms are replaced in a preferably linear alkyl by oxygen atoms preferably separated from one another by several (especially 2) carbon atoms so that they form a repeating group, if need be multi-repeating group $(O\text{-}CH_2\text{-}CH_2\text{-})_q$, wherein q = 1 to 7.

Especially preferred as R_3 or R_4, apart from acyl, is lower alkyl, particlularly methyl or ethyl; lower alkoxycarbonyl-lower alkyl, especially methoxycarbonylmethyl or 2-(tert-butoxycarbonyl)ethyl; carboxy-lower alkyl, especially carboxymethyl or 2-carboxyethyl; or cyano-lower alkyl, especially 2-cyanoethyl.

An acyl radical R_3 or R_4 with up to 30 carbon atoms derives from a carboxylic acid, functionally modified if need be, an organic sulfonic acid, or a phosphoric acid, such as pyro- or orthophosphoric acid, esterified if need be.

An acyl designated Ac^1 and derived from a carboxylic acid, functionally modified if need be, is especially one of the subformula Y-C(=W)-, wherein W is oxygen, sulfur, or imino and Y is hydrogen, hydrocarbyl R° with up to 29 carbon atoms, hydrocarbyloxy R°-O-, an amino group or a substituted amino group, especially one of the formula $R^\circ HN$- or $R^\circ R^\circ N$- (wherein the R° radicals may be identical or different from one another).

The hydrocarbyl (hydrocarbon radical) R° is an acyclic (aliphatic), carbocyclic, or carbocyclic-acyclic hydrocarbon radical, with up to 29 carbon atoms each, especially up to 18, and preferably up to 12 carbon atoms, and is saturated or unsaturated, unsubstituted or substituted. Instead of one, two, or more carbon atoms, it may contain identical or different heteroatoms, such as especially oxygen, sulfur, and nitrogen in the acyclic and/or cyclic part; in the latter case, it is described as a heterocyclic radical (heterocyclyl radical) or a heterocyclic-acyclic radical.

Unsaturated radicals are those which contain one or more, especially conjugated and/or isolated, multiple bonds (double or triple bonds). The term cyclic radicals includes also aromatic and non-aromatic radicals with conjugated double bonds, for example those wherein at least one 6-member carbocyclic or a 5- to 8-member heterocyclic ring contains the maximum number of non-cumulative double bonds. Carbocyclic radicals, wherein at least one ring is present as a 6-member aromatic ring (i.e. a benzene ring), are defined as aryl radicals.

An acyclic unsubstituted hydrocarbon radical R° is especially a straight-chained or branched lower alkyl-, lower alkenyl-, lower alkadienyl-, or lower alkinyl radical. Lower alkyl R° is, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl or tert-butyl, and also n-pentyl, isopentyl, n-hexyl, isohexyl and n-heptyl; lower alkenyl is, for example, allyl, propenyl, isopropenyl, 2- or 3-methallyl and 2- or 3-butenyl; lower alkadienyl is, for example, 1-penta-2,4-dienyl; lower alkinyl is, for example, propargyl or 2-butinyl. In corresponding unsaturated radicals, the double bond is especially located in a position higher than the α-position in relation to the free valency.

A carbocyclic hydrocarbon radical R° is especially a mono-, bi-, or polycyclic cycloalkyl-, cycloalkenyl-, or cycloalkadienyl radical, or a corresponding aryl radical. Preference is for radicals with a maximum of 14, especially 12, ring-carbon atoms and 3- to 8-, preferably 5- to 7-, and most especially 6-member rings which can also carry one or more, for example two, acyclic radicals, for example those named above, especially the lower alkyl radicals, or other carbocyclic radicals. Carbocyclic-acyclic radicals are those in which an acyclic radical, especially one with a maximum of 7, preferably a maximum of 4 carbon atoms, such as especially methyl, ethyl and vinyl, carries one or more carbocyclic, if need be aromatic radicals of the above definition. Special mention is made of cycloalkyl-lower and aryl-lower alkyl radicals, as well as their analogues which are unsaturated in the ring and/or chain, and which carry the ring at the terminal carbon atom of the chain.

Cycloalkyl R° has most especially from 3 up to and including 10 carbon atoms and is, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl, as well as bicyclo[2,2,2]octyl, 2-bicyclo[2,2,1]heptyl, and adamantyl, which may also be substituted by 1, 2, or more, for example lower, alkyl radicals, especially methyl radicals;

cycloalkenyl is for example one of the monocyclic cycloalkyl radicals already named which carries a double bond in the 1-, 2-, or 3 position. Cycloalkyl-lower alkyl or -lower alkenyl is for example a -methyl, -1- or -2-ethyl, -1- or -2-vinyl, -1-, -2-, or -3-propyl or -allyl substituted by one of the above-named cycloalkyl radicals, those substituted at the end of the linear chain being preferred.

An aryl radical R^0 is most especially a phenyl, also a naphthyl, such as 1- or 2-naphthyl, a biphenylyl, such as especially 4-biphenylyl, and also an anthryl, fluorenyl and azulenyl, as well as their aromatic analogues with one or more saturated rings. Preferred aryl-lower alkyl and -lower alkenyl radicals are, for example, phenyl-lower alkyl or phenyl-lower alkenyl with a terminal phenyl radical, such as for example benzyl, phenethyl, 1-, 2-, or 3-phenylpropyl, diphenylmethyl (benzhydryl), trityl, and cinnamyl, and also 1- or 2-naphthylmethyl. Aryl may be unsubstituted or substituted.

Heterocyclic radicals, including heterocyclic-acyclic radicals, are especially monocyclic, but also bi- or polycyclic, aza-, thia-, oxa-, thiaza-, oxaza-, diaza-, triaza-, or tetrazacyclic radicals of an aromatic character, as well as corresponding heterocyclic radicals of this type which are partly or most especially wholly saturated; if need be, for example as in the case of the above-mentioned carbocyclic or aryl radicals, these radicals may carry further acyclic, carbocyclic, or heterocyclic radicals and/or may be mono-, di-, or polysubstituted by functional groups. The acyclic part in heterocyclic-acyclic radicals has for example the meaning indicated for the corresponding carbocyclic-acyclic radicals. Most especially they are unsubstituted or substituted monocyclic radicals with a nitrogen, oxygen, or sulfur atom, such as 2-aziridinyl, and especially aromatic radicals of this type, such as pyrrolyl, for example 2-pyrrolyl or 3-pyrrolyl, pyridyl, for example 2-, 3-, or 4-pyridyl, and also thienyl, for example 2- or 3-thienyl, or furyl, for example 2-furyl; analogous bicyclic radicals with an oxygen, sulfur, or nitrogen atom are, for example, indolyl, typically 2- or 3-indolyl, quinolyl, typically 2- or 4-quinolyl, isoquinolyl, typically 3- or 5-isoquinolyl, benzofuranyl, typically 2-benzofuranyl, chromenyl, typically 3-chromenyl, or benzothienyl, typically 2- or 3-benzothienyl; preferred monocyclic and bicyclic radicals with several heteroatoms are, for example, imidazolyl, typically 2-imidazolyl, pyrimidinyl, typically 2-or 4-pyrimidinyl, oxazolyl, typically 2-oxazolyl, isoxazolyl, typically 3-isoxazolyl, or thiazolyl, typically 2-thiazolyl, and benzimidazolyl, typically 2-benzimidazolyl, benzoxazolyl, typically 2-benzoxazolyl, or

quinazolyl, typically 2-quinazolinyl. Appropriate partially or, especially, completely saturated analogous radicals may also be considered, such as 2-tetrahydrofuryl, 4-tetrahydrofuryl, 2- or 3-pyrrolidyl, 2-, 3-, or 4-piperidyl, and also 2-or 3-morpholinyl, 2- or 3-thiomorpholinyl, 2-piperazinyl, and N,N'-bis-lower alkyl-2-piperazinyl radicals. These radicals may also carry one or more acyclic, carbocyclic, or heterocyclic radicals, especially those mentioned hereinabove. Heterocyclic-acyclic radicals are especially derived from acyclic radicals with a maximum of 7, preferably a maximum of 4 carbon atoms, for example those named hereinabove, and may carry one, two, or more heterocyclic radicals, for example those named hereinabove, the ring possibly being linked to the aliphatic chain also by one of its nitrogen atoms.

As already mentioned, a hydrocarbyl (including a heterocyclyl) may be substituted by one, two, or more identical or different substituents (functional groups); one or more of the following substituents may be considered: lower alkyl; free, etherified and esterified hydroxyl groups; carboxy groups and esterified carboxy groups; mercapto- and lower alkylthio- and, if need be, substituted phenylthio groups; halogen atoms, typically chlorine and fluorine, but also bromine and iodine; *halogen-lower alkyl groups;* oxo groups which are present in the form of formyl (i.e. aldehydo) and keto groups, also as corresponding acetals or ketals; azido groups; nitro groups; cyano groups; primary, secondary and preferably tertiary amino groups, amino-lower alkyl, mono- or disubstituted amino-lower alkyl, primary or secondary amino groups protected by conventional protecting groups (especially lower alkoxycarbonyl, typically tert-butoxycarbonyl) lower alkylenedioxy, and also free or functionally modified sulfo groups, typically sulfamoyl or sulfo groups present in free form or as salts. The hydrocarbyl radical may also carry carbamoyl, ureido, or guanidino groups, which are free or which carry one or two substituents, and cyano groups. The above use of the word "groups" is taken to imply also an individual group.

Halogen-lower alkyl contains preferably 1 to 3 halogen atoms; preferred is trifluoromethyl or chloromethyl.

An etherified hydroxyl group present in the hydrocarbyl as substituent is, for example, a lower alkoxy group, typically the methoxy-, ethoxy-, propoxy-, isopropoxy-, butoxy-, and tert-butoxy group, which may also be substituted, especially by (i) heterocyclyl, whereby

heterocyclyl can have preferably 4 to 12 ring atoms, may be unsaturated, or partially or wholly saturated, is mono- or bicyclic, and may contain up to three heteroatoms selected from nitrogen, oxygen, and sulfur, and is most especially pyrrolyl, for example 2-pyrrolyl or 3-pyrrolyl, pyridyl, for example 2-, 3- or 4-pyridyl, and also thienyl, for example 2- or 3-thienyl, or furyl, for example 2-furyl, indolyl, typically 2- or 3-indolyl, quinolyl, typically 2- or 4-quinolyl, isoquinolyl, typically 3- or 5-isoquinolyl, benzofuranyl, typically 2-benzofuranyl, chromenyl, typically 3-chromenyl, benzothienyl, typically 2- or 3-benzothienyl; imidazolyl, typically 1- or 2-imidazolyl, pyrimidinyl, typically 2-or 4-pyrimidinyl, oxazolyl, typically 2-oxazolyl, isoxazolyl, typically 3-isoxazolyl, thiazolyl, typically 2-thiazolyl, benzimidazolyl, typically 2-benzimidazolyl, benzoxazolyl, typically 2-benzoxazolyl, quinazolyl, typically 2-quinazolinyl, 2-tetrahydrofuryl, 4-tetrahydrofuryl, 2- or 4-tetrahydropyranyl, 1-, 2- or 3-pyrrolidyl, 1-, 2-, 3-, or 4-piperidyl, 1-, 2-or 3-morpholinyl, 2- or 3-thiomorpholinyl, 2-piperazinyl or N,N'-bis-lower alkyl-2-piperazinyl; and also (ii) by halogen atoms, for example mono-, di-, or polysubstituted especially in the 2-position, as in the 2,2,2-trichloroethoxy, 2-chloroethoxy, or 2-iodoethoxy radical, or (iii) by hydroxy or (iv) lower alkoxy radicals, each preferably monosubstituted, especially in the 2-position, as in the 2-methoxyethoxy radical. Such etherified hydroxyl groups are also unsubstituted or substituted phenoxy radicals and phenyl-lower alkoxy radicals, such as especially benzyloxy, benzhydryloxy, and triphenylmethoxy (trityloxy), as well as heterocyclyloxy radicals, wherein heterocyclyl can have preferably 4 to 12 ring atoms, may be unsaturated, or partially or wholly saturated, is mono- or bicyclic, and may contain up to three heteroatoms selected from nitrogen, oxygen, and sulfur, and is most especially pyrrolyl, for example 2-pyrrolyl or 3-pyrrolyl, pyridyl, for example 2-, 3- or 4-pyridyl, and also thienyl, for example 2- or 3-thienyl, or furyl, for example 2-furyl, indolyl, typically 2- or 3-indolyl, quinolyl, typically 2- or 4-quinolyl, isoquinolyl, typically 3- or 5-isoquinolyl, benzofuranyl, typically 2-benzofuranyl, chromenyl, typically 3-chromenyl, benzothienyl, typically 2- or 3-benzothienyl; imidazolyl, typically 1- or 2-imidazolyl, pyrimidinyl, typically 2- or 4-pyrimidinyl, oxazolyl, typically 2-oxazolyl, isoxazolyl, typically 3-isoxazolyl, thiazolyl, typically 2-thiazolyl, benzimidazolyl, typically 2-benzimidazolyl, benzoxazolyl, typically 2-benzoxazolyl, quinazolyl, typically 2-quinazolinyl, 2-tetrahydrofuryl, 4-tetrahydrofuryl, 2- or 4-tetrahydropyranyl, 1-, 2- or 3-pyrrolidyl, 1-, 2-, 3-, or 4-piperidyl, 1-, 2- or 3-morpholinyl, 2- or 3-thiomorpholinyl, 2-piperazinyl or N,N'-bis-lower alkyl-2-piperazinyl; such as especially 2- or 4-tetrahydropyranyloxy.

Etherified hydroxyl groups in this context are taken to include silylated hydroxyl groups, typically for example tri-lower alkylsilyloxy, typically trimethylsilyloxy and dimethyl-tert-butylsilyloxy, or phenyldi-lower alkylsilyloxy and lower alkyl-diphenylsilyloxy.

An esterified hydroxyl group present in the hydrocarbyl as a substituent is, for example, lower alkanoyloxy.

A carboxyl group present in the hydrocarbyl as a substituent is one in which the hydrogen atom is replaced by one of the hydrogen radicals characterised hereinabove, preferably a lower alkyl- or phenyl-lower alkyl radical; an example of an esterified carboxyl group is lower alkoxycarbonyl or phenyl-lower alkoxycarbonyl substituted if need be in the phenyl part, especially the methoxy, ethoxy, tert-butoxy, and benzyloxycarbonyl group, as well as a lactonised carboxyl group.

A primary amino group $-NH_2$ as substituent of the hydrocarbyls may also be present in a form protected by a conventional protecting group. A secondary amino group carries, instead of one of the two hydrogen atoms, a hydrocarbyl radical, preferably an unsubstituted one, typically one of the above-named, especially lower alkyl, and may also be present in protected form.

A tertiary amino group present in the hydrocarbyl as substituent carries 2 different or, preferably, identical hydrocarbyl radicals (including the heterocyclic radicals), such as the unsubstituted hydrocarbyl radicals characterised hereinabove, especially lower alkyl.

A preferred amino group is one with the formula $R_6(R_7)N-$, wherein R_6 and R_7 are independently in each case hydrogen, unsubstituted acyclic C_1-C_7-hydrocarbyl (such as especially C_1-C_4alkyl or C_2-C_4alkenyl) or monocyclic aryl, aralkyl, or aralkenyl, substituted if necessary by C_1-C_4-alkyl, C_1-C_4-alkoxy, halogen, and/or nitro, and having a maximum of 10 carbon atoms, where the carbon-containing radicals may be interlinked through a carbon-carbon bond or an oxygen atom, a sulfur atom, or a nitrogen atom substituted if necessary by hydrocarbyl. In such a case, they form a nitrogen-containing heterocyclic ring with the nitrogen atom of the amino group. The following are examples of especially preferred disubstituted amino groups: di-lower alkylamino, typically dimethylamino or diethylamino,

pyrrolidino, imidazol-1-yl, piperidino, piperazino, 4-lower alkylpiperazino, morpholino, thiomorpholino and piperazino or 4-methylpiperazino, as well as diphenylamino and dibenzylamino substituted if need be, especially in the phenyl part, for example by lower-alkyl, lower-alkoxy, halogen, and/or nitro; of the protected groups, especially lower alkoxy-carbonylamino, typically tert-butoxycarbonylamino, phenyl-lower alkoxycarbonylamino, typically 4-methoxybenzyloxycarbonylamino, and 9-fluorenylmethoxycarbonylamino.

Amino-lower alkyl is most especially substituted in the 1-position of the lower alkyl chain by amino and is especially aminomethyl.

Mono- or disubstituted amino-lower alkyl is amino-lower alkyl substituted by one or two radicals, wherein amino-lower alkyl is most especially substituted by amino in the 1-position of the lower alkyl chain and is especially aminomethyl; the amino substituents here are preferably (if 2 substituents are present in the respective amino group independently of one another) from the group comprising lower alkyl, such as especially methyl, ethyl or n-propyl, hydroxy-lower alkyl, typically 2-hydroxyethyl, C_3-C_8cycloalkyl, especially cyclohexyl, amino-lower alkyl, typically 3-aminopropyl or 4-aminobutyl, N-mono- or N,N-di(lower alkyl)-amino-lower alkyl, typically 3-(N,N-dimethylamino)propyl, amino, N-mono- or N,N-di-lower alkylamino and N-mono- or N,N-di-(hydroxy-lower alkyl)amino.

Disubstituted amino-lower alkyl is also a 5 or 6-membered, saturated or unsaturated heterocyclyl bonded to lower alkyl via a nitrogen atom (preferably in the 1-position) and having 0 to 2, especially 0 or 1, other heteroatoms selected from oxygen, nitrogen, and sulfur, which is unsubstituted or substituted, especially by one or two radicals from the group comprising lower alkyl, typically methyl, and also oxo. Preferred here is pyrrolidino (1-pyrrolidinyl), piperidino (1-piperidinyl), piperazino (1-piperazinyl), 4-lower alkylpiperazino, typically 4-methylpiperazino, imidazolino (1-imidazolyl), morpholino (4-morpholinyl), or also thiomorpholino, S-oxo-thiomorpholino, or S,S-dioxothiomorpholino.

Lower alkylenedioxy is especially methylenedioxy.

A carbamoyl group carrying one or two substituents is especially aminocarbonyl (carbamoyl) which is substitiuted by one or two radicals at the nitrogen; the amino substituents here are

preferably (if 2 substituents are present in the respective amino group independently of one another) from the group comprising lower alkyl, such as especially methyl, ethyl or n-propyl, hydroxy-lower alkyl, typically 2-hydroxyethyl, C_3-C_8cycloalkyl, especially cyclohexyl, amino-lower alkyl, typically 3-aminopropyl or 4-aminobutyl, N-mono- or N,N-di(lower alkyl)-amino-lower alkyl, typically 3-(N,N-dimethylamino)propyl, amino, N-mono- or N,N-di-lower alkylamino and N-mono- or N,N-di-(hydroxy-lower alkyl)amino; disubstituted amino in aminocarbamoyl is also a 5 or 6-membered, saturated or unsaturated heterocyclyl with a bonding nitrogen atom and 0 to 2, especially 0 or 1, other heteroatoms selected from oxygen, nitrogen, and sulfur, which is unsubstituted or substituted, especially by one or two radicals from the group comprising lower alkyl, typically methyl, and also oxo. Preferred here is pyrrolidino (1-pyrrolidinyl), piperidino (1-piperidinyl), piperazino (1-piperazinyl), 4-lower alkylpiperazino, typically 4-methylpiperazino, imidazolino (1-imidazolyl), morpholino (4-morpholinyl), or also thiomorpholino, S-oxo-thiomorpholino, or S,S-dioxothiomorpholino.

An acyl derived from an organic sulfonic acid, which is designated Ac^2, is especially one with the subformula R°-SO_2-, wherein R° is a hydrocarbyl as defined above in the general and specific meanings, the latter also being generally preferred here. Especially preferred is lower alkylphenylsulfonyl, especially 4-toluenesulfonyl.

An acyl derived from a phosphoric acid, esterified if necessary, which is designated Ac^3, is especially one with the subformula $R^\circ O(R^\circ O)P(=O)$-, wherein the radicals R° are, independently of one another, as defined in the general and specific meanings indicated above.

Reduced data on substituents given hereinbefore and hereinafter are considered to be preferences.

Preferred compounds of formula I according to the invention are, for example, those wherein R^0 has the following preferred meanings: lower alkyl, especially methyl or ethyl, amino-lower alkyl, wherein the amino group is unprotected or is protected by a conventional amino protecting group – especially by lower alkoxycarbonyl, typically tert-lower alkoxy-carbonyl, for example tert-butoxycarbonyl – e.g. aminomethyl, R,S-, R- or preferably S-1-aminoethyl, tert-butoxycarbonylaminomethyl or R,S-, R-, or preferably S-1-(tert-butoxy-

carbonylamino)ethyl, carboxy-lower alkyl, typically 2-carboxyethyl, lower alkoxycarbonyl-lower alkyl, typically 2-(tert-butoxycarbonyl)ethyl, cyano-lower alkyl, typically 2-cyanoethyl, tetrahydropyranyloxy-lower alkyl, typically 4-(tetrahydropyranyl)-oxymethyl, morpholino-lower alkyl, typically 2-(morpholino)ethyl, phenyl, lower alkylphenyl, typically 4-methylphenyl, lower alkoxyphenyl, typically 4-methoxyphenyl, imidazolyl-lower alkoxyphenyl, typically 4-[2-(imidazol-1-yl)ethyl)oyxphenyl, carboxyphenyl, typically 4-carboxyphenyl, lower alkoxy-carbonylphenyl, typically 4-ethoxycarbonylphenyl or 4-methoxyphenyl, halogen-lower alkylphenyl, typically 4-chloromethylphenyl, pyrrolidinophenyl, typically 4-pyrrolidinophenyl, imidazol-1-ylphenyl, typically 4-(imidazolyl-1-yl)phenyl, piperazinophenyl, typically 4-piperazinophenyl, (4-lower alkylpiperazino)phenyl, typically 4-(4-methylpiperazino)phenyl, morpholinophenyl, typically 4-morpholinophenyl, pyrrolidino-lower alkylphenyl, typically 4-pyrrolidinomethylphenyl, imidazol-1-yl-lower alkylphenyl, typically 4-(imidazolyl-1-yl-methyl)phenyl, piperazino-lower alkylphenyl, typically 4-piperazinomethylphenyl, (4-lower alkylpiperazinomethyl)-phenyl, typically 4-(4-methylpiperazinomethyl)phenyl, morpholino-lower alkylphenyl, typically 4-morpholinomethylphenyl, piperazinocarbonylphenyl, typically 4-piperazinocarbonylphenyl, or (4-lower alkyl-piperazino)phenyl, typically 4-(4-methylpiperazino)phenyl.

Preferred acyl radicals Ac^1 are acyl radicals of a carboxylic acid which are characterised by the subformula R°-CO-, wherein R° has one of the above general and preferred meanings of the hydrocarbyl radical R°. Especially preferred radicals R° here are lower alkyl, especially methyl or ethyl, amino-lower alkyl, wherein the amino group is unprotected or protected by a conventional amino protecting group, especially by lower alkoxycarbonyl, typically tert-lower alkoxycarbonyl, for example tert-butoxycarbonyl, e.g. aminomethyl, R,S-, R-, or preferably S-1-aminoethyl, tert-butoxycarbonylaminomethyl or R,S-, R-, or preferably S-1-(tert-butoxycarbonylamino)ethyl, carboxy-lower alkyl, typically 2-carboxyethyl, lower alkoxycarbonyl-lower alkyl, typically 2-(tert-butoxycarbonyl)ethyl, tetrahydropyranyloxy-lower alkyl, typically 4-(tetrahydropyranyl)oxymethyl, phenyl, imidazolyl-lower alkoxyphenyl, typically 4-[2-(imidazol-1-yl)ethyl]oyxphenyl, carboxyphenyl, typically 4-carboxyphenyl, lower alkoxycarbonylphenyl, typically 4-ethoxycarbonylphenyl, halogen-lower alkylphenyl, typically 4-chloromethylphenyl, imidazol-1-ylphenyl, typically 4-(imidazolyl-1-yl)phenyl, pyrrolidino-lower alkylphenyl, typically 4-pyrrolidinomethylphenyl, piperazino-lower alkylphenyl, typically 4-piperazinomethylphenyl, (4-lower alkylpiperazinomethyl)phenyl, typically 4-(4-methyl-

piperazinomethyl)phenyl, morpholino-lower alkylphenyl, typically 4-morpholinomethylphenyl, piperazinocarbonylphenyl, typically 4-piperazinocarbonylphenyl, or (4-lower alkylpiperazino)phenyl, typically 4-(4-methylpiperazino)phenyl.

A further preferred Acyl Ac^1 is derived from monoesters of carbonic acid and is characterised by the subformula R°-O-CO-. The lower alkyl radicals, especially tert-butyl, are especially preferred hydrocarbyl radicals R° in these derivatives.

Another preferred Acyl Ac^1 is derived from amides of carbonic acid (or also thiocarbonic acid) and is characterised by the formula R°HN-C(=W)- or R°R°N-C(=W)-, wherein the radicals R° are, independently of one another, as defined above and W is sulfur and especially oxygen. In particular, compounds are preferred wherein Ac^1 is a radical of formula R°HN-C(=W)-, wherein W is oxygen and R° has one of the following preferred meanings: morpholino-lower alkyl, typically 2-morpholinoethyl, phenyl, lower alkoxyphenyl, typically 4-methoxyphenyl or 4-ethoxyphenyl, carboxyphenyl, typically 4-carboxyphenyl, or lower alkoxycarbonylphenyl, typically 4-ethoxycarbonylphenyl.

A preferred acyl Ac^2 of subformula R°-SO_2-, wherein R° is a hydrocarbyl as defined in the above general and specific meanings, is lower alkylphenylsulfonyl, typically 4-toluenesulfonyl.

If p is 0, the nitrogen atom bonding R_3 is uncharged. If p is 1, then R_4 must also be present, and the nitrogen atom bonding R_3 and R_4 (quaternary nitrogen) is then positively charged.

The definitions for an aliphatic, carbocyclic, or carbocyclic-aliphatic radical with up to 29 carbon atoms each, or for a heterocyclic or heterocyclic-aliphatic radical with up to 20 carbon atoms each and up to 9 heteroatoms each, or acyl with up to 30 carbon atoms each, preferably match the definitions given for the corresponding radicals R_3 and R_4. Especially preferred is R_5 lower alkyl, especially methyl, or most especially hydrogen.

Z is especially lower alkyl, most especially methyl.

If the two bonds indicated by wavy lines are missing in ring A, then no double bonds (tetra-hydrogenated derivatives) are present between the carbon atoms characterised in formula I by the numbers 1, 2, 3, and 4, but only single bonds, whereas ring B is aromatic (double bonds between the carbon atoms characterised in formula I by 8 and 9 and those characterised by 10 and 11). If the two bonds indicated by wavy lines are missing in ring B, then no double bonds (tetra-hydrogenated derivatives) are present between the carbon atoms characterised in formula I by the numbers 8, 9, 10, and 11, but only single bonds, whereas ring A is aromatic (double bonds between the carbon atoms characterised in formula I by 1 and 2 and those characterised by 3 and 4). If the total of four bonds indicated by wavy lines are missing in rings A and B, and are replaced by a total of 8 hydrogen atoms, then no double bonds (octa-hydrogenated derivatives) are present between the carbon atoms numbered 1, 2, 3, 4, 8, 9, 10, and 11 in formula I, but only single bonds.

By their nature, the compounds of the invention may also be present in the form of pharmaceutically, i.e. physiologically, acceptable salts, provided they contain salt-forming groups. For isolation and purification, pharmaceutically unacceptable salts may also be used. For therapeutic use, only pharmaceutically acceptable salts are used, and these salts are preferred.

Thus, compounds of formula I having free acid groups, for example a free sulfo, phosphoryl or carboxyl group, may exist as a salt, preferably as a physiologically acceptable salt with a salt-forming basic component. These may be primarily metal or ammonium salts, such as alkali metal or alkaline earth metal salts, for example sodium, potassium, magnesium or calcium salts, or ammonium salts with ammonia or suitable organic amines, especially tertiary monoamines and heterocyclic bases, for example triethylamine, tri-(2-hydroxyethyl)-amine, N-ethylpiperidine or N,N'-dimethylpiperazine.

Compounds of the invention having a basic character may also exist as addition salts, especially as acid addition salts with inorganic and organic acids, but also as quaternary salts. Thus, for example, compounds of formula I which have a basic group, such as an amino group, as a substituent may form acid addition salts with common acids. Suitable acids are, for example, hydrohalic acids, e.g. hydrochloric and hydrobromic acid, sulfuric

acid, phosphoric acid, nitric acid or perchloric acid, or aliphatic, alicyclic, aromatic or heterocyclic carboxylic or sulfonic acids, such as formic, acetic, propionic, succinic, glycolic, lactic, malic, tartaric, citric, fumaric, maleic, hydroxymaleic, oxalic, pyruvic, phenylacetic, benzoic, p-aminobenzoic, anthranilic, p-hydroxybenzoic, salicylic, p-aminosalicylic acid, pamoic acid, methanesulfonic, ethanesulfonic, hydroxyethanesulfonic, ethylenedisulfonic, halobenzenesulfonic, toluenesulfonic, naphthalenesulfonic acids or sulfanilic acid, and also methionine, tryptophan, lysine or arginine, as well as ascorbic acid.

In view of the close relationship between the novel compounds (especially of formula I) in free form and in the form of their salts, including those salts that can be used as intermediates, for example in the purification or identification of the novel compounds, and of their solvates, any reference hereinbefore and hereinafter to the free compounds is to be understood as referring also to the corresponding salts, and the solvates thereof, for example hydrates, as appropriate and expedient.

The compounds of formula I, especially those wherein R_5 is hydrogen, possess valuable pharmacological properties, for example they markedly inhibit the enzyme protein kinase C, especially protein kinase C-α. Protein kinase C, which is dependent on phospholipids and calcium, occurs in the cells in several forms and is involved in various fundamental processes, such as signal transduction, proliferation, and differentiation, as well as the secretion of hormones and neurotransmitters. This enzyme is activated either by a receptor-mediated hydrolysis of phospholipids in the cell membrane or by a direct interaction with certain tumour-promoting substances. The sensitivity of the cells to receptor-mediated signal transduction can be substantially influenced by changes in the activity of protein kinase C (as signal transmitter). Compounds which are capable of influencing protein kinase C may be used as tumour-suppressant, anti-inflammatory, immunomodulatory, and antibacterial substances, and may even be of interest for the treatment of atherosclerosis and diseases of the cardiovascular and central nervous systems.

The inhibitory effect on protein kinase C can be measured using, for example, protein kinase C from pig brain, purified according to the procedure described by T. Uchida and C.R. Filburn in J. Biol. Chem. 259, 12311-4 (1984). The inhibitory effect of the compounds of formula I on protein kinase C is determined according to the method of D. Fabbro et al.,

Arch. Biochem. Biophys. 239, 102-111 (1985). In this test, the compounds of formula I inhibit protein kinase C.

Instead of the protein kinase C specified in the above test, recombinant PKC isozymes are preferably used. Recombinant PKC isozymes are cloned, expressed, and purified as follows:

The preparation of different proteins using baculoviruses, their cloning and isolation from Sf9 insect cells are carried out as described by M.D. Summers und G.E. Smith, "A manual method for baculovirus vectors and insect cell culture procedure", Texas Agricul. Exptl. Station Bull. (1987), 1555. Recombinant viruses for the expression of PKC-α (cattle), PKC-β1 (humans), PKC-β2 (humans), and PKC-γ (human/bovine hybrid) in Sf9 cells are constructed and isolated as described by Stabel et al. [S. Stabel, M. Liyanage and D. Frith, "Expression of protein kinase C isozymes in insect cells and isolation of recombinant protein", Meth. Neurosc. (1993)]. PKC isozymes are prepared in Sf9 cells as indicated by Stabel et al. (see above), and the enzymes purified according to the method described in the publication of McGlynn et al. [E. McGlynn, J. Liebetanz, S. Reutener, J. Wood, N.B. Lydon, H. Hofstetter, M. Vanek, T. Meyer und D. Fabbro, "Expression and partial characterization of rat protein kinase C-δ and protein kinase C-ζ in insect cells using recombinant baculovirus", J. Cell. Biochem. 49, 239-250 (1992)]. For the generation of recombinant PKC-δ (rat), PKC-ε (rat), PKC-ζ (rat) and PKC-η (mouse), and their expression and purification, the procedure described by Liyanage et al. ["Protein kinase C group B members PKC-δ, -ε, -ζ and PKC-λ: Comparison of properties of recombinant proteins in vitro and in vivo", Biochem. J. 283, 781-787 (1992)] or McGlynn et al. (see above) is followed, together with the transfer vector pAC360 for the expression of PKC-η [V. Luckow und M.D. Summers, "Trends in the development of baculovirus expression", Biotechnology 6, 47-55 (1988)].

Protamine sulfate, which is phosphorylated in the absence of co-factors (lipids and calcium), is used as a substrate for measuring the activity of the recombinant PKC-isozymes obtained by means of the above method. The activity of the enzymes reflects the transfer of ^{33}P from γ-[^{33}P]-ATP to protamine sulfate. Protamine sulfate is a mixture of polypeptides, each containing four carboxy-terminal arginine radicals. The phosphate incorporation is

measured under the following conditions: 100 µl of the reaction mixture in the final preparation contains 20 mM TRIS-HCl pH 7.4, 10 mM $Mg[NO_3]_2$, 0.5 mg/ml protamine sulfate, 10 µM ATP (0.1 µCi γ-[^{32}P]-ATP; 10 Ci/mol; Amersham, Little Chalfont, United Kingdom), various concentrations of the inhibitory substances, and 0.5–2.5 U (units; a unit is the amount of enzyme which transfers a nanomol ^{32}P from the above-mentioned γ-[^{32}P]-ATP to histone H1 [Sigma, Type V-S] in one minute per milligramm of protein) of enzymes. The reaction is started by the addition of enzymes and transfer to 32°C. The reaction time is 20 minutes. Afterwards, the reaction is stopped, dropping aliquots of 50 µl on P81 chromatography paper (Whatman, Maidstone, United Kingdom). After removal of unbound γ-[^{32}P]-ATP and nucleotide fragments by means of washing procedures described by J.J. Witt and R. Roskoski, "Rapid protein kinase assay using phospho-cellulose-paper absorption", Anal. Biochem. 66, 253-58 (1975), the substrate phosphorylation is measured by scintillation. In this test, for example, compounds of formula I inhibit PKC-α at a concentration of IC_{50} between about 0.001 and 5 µmol/litre. In particular, compounds of formula I wherein R_5 is hydrogen show an inhibitory effect between 0.001 and 1 µM.

As a rule, the compounds of formula I require a far higher concentration, however, to inhibit other enzymes, for example EGF-receptor protein tyrosine kinase. This illustrates the selectivity of the compounds of formula I. For example, the intracellular domain of the EGR-receptor protein tyrosine kinase is used (see Buchdunger, E., et al., Proc. Natl. Acad. Sci USA 91, 2334-8 (1994)). The effect of the compounds on the cellular tyrosine phosphorylation induced by EGF and PDGF can be measured in human A-431 cells and BALB/c 3T3 mouse cells (see Trinks, U., et al., J. Med. Chem. 37, 1015-1027 (1994)).

Especially surprising, however, is the very good efficacy shown by compounds of the present invention in the inhibition of $p34^{cdc2}$/cycline B^{cdc13}-kinase (CDK1), which suggests a corresponding efficacy also for example versus CDK1- and CDK2-kinase in humans. This opens up the possibility of treating not only proliferative diseases, but also for example fungal infections in humans. The inhibition of $p34^{cdc2}$/cycline B^{cdc13}-kinase can be measured as follows:

10 µM 1-methyladenine is used to trigger the M-phase in starfish oocytes, which are then frozen in liquid nitrogen and stored at -80 °C. If required, the oocytes are homogenised and

centrifuged, as described in D. Arion et al., Cell 55, 371-8 (1988) and V. Rialet and L. Meijer, Anticancer Res. 11, 1581-90 (1991). To purify the $p34^{cdc2}$/cycline B^{cdc13}-kinase, the supernatant oocytes are added to $p9^{CKShs}$-sepharose beads prepared from recombinant human protein $p9^{CKShs}$, as described in L. Azzi et al., Eur. J. Biochem. 203, 353-360 (1992). After 30 minutes at 4°C under constant rotation, the beads are thoroughly washed, and the active $p34^{cdc2}$/cycline B^{cdc13}-kinase is eluted with free protein $p9^{CKShs}$ (3 mg/ml). The eluted kinase is tested using histone H1 as a substrate, as described in L. Meijer et al., EMBO J. 8, 2275-82 (1989) und EMBO J. 10, 1545-54 (1991). In this test, the compounds of formula I and their pharmaceutically acceptable salts show an inhibitory action at the nanomolar level. For example, the compound 1,2,3,4-tetrahydrostaurosporine (Example 1, compound 1a) shows an IC_{50} (the concentration required to reduce activity by 50%) of 0.5 nM.

The $p34^{cdc2}$/cycline B^{cdc13}-kinase enzyme, along with other cdc2-related kinases, regulates certain phases of cell division, especially the transition from the G_1 phase to the S phase, and most especially the transition from the G_2 phase to the M phase.

The cycle of a eukaryotic cell runs from the interphase to the M phase. The interphase is associated with cell growth. This phase in turn consists of the G_1 phase, the S phase, and the G_2 phase, in order of activity. In the G_1 phase (G = gap), biosynthetic processes take place in the cell. The S phase (synthesis phase) is characterised by DNA replication. After this the cell enters the G_2 phase, which ends with the start of mitosis. The M phase for its part is characterised by division of the cell nucleus (mitosis) and division of the cytoplasm (cytokinesis) in this order.

As may already be expected on the basis of the inhibitory action on protein kinase C outlined above, the compounds of formula I show antiproliferative properties which are directly demonstrated in the following additional test. Here the inhibitory action of the compounds of formula I is determined with regard to the growth of human T24 bladder carcinoma cells. These cells are incubated in "Eagle's minimal essential medium", to which 5 % (v/v) fetal calf serum has been added, using a humidified incubator at 37°C and 5 % by volume of CO_2 in air. The carcinoma cells (1000–1500) are transferred to 96-well microtitre plates and incubated overnight under the said conditions. The test substance is added on day 1 in serial dilutions. The plates are incubated for 5 days under the said conditions.

During this time, the control cultures undergo at least 3 cell divisions. After incubation, the cells are fixed with 3.3% (w/v) aqueous glutaraldehyde solution, washed with water, and stained with 0.05% (w/v) aqueous methylene blue solution. After washing, the stain is eluted with 3% (w/v) aqueous hydrochloric acid. Thereafter, the optical density (OD) per well, which is directly proportional to the number of cells, is measured using a photometer (Titertek multiskan) at 665 nm. The IC_{50} values are calculated with a computer system using the formula

$$\frac{OD_{665}\text{ (test)} - OD_{665}\text{ (start)} \times 100}{OD_{665}\text{ (control)} - OD_{665}\text{ (start)}}$$

The IC_{50} value is defined as the concentration of active substance at which the number of cells per well is reduced to 50% of the number of cells in the control culture at the end of the incubation period. The IC_{50} values determined in this way for the compounds of formula I lie between about 0.001 and 10 μmol/litre, preferably between about 0.005 and 10 μmol/litre, especially between about 0.008 and 5 μmol/litre.

The antitumour efficacy of the compounds of the invention can also be demonstrated *in vivo* as follows:

Male or female BALB/c nu/nu mice (10 to 12 mice per cage type III; Novartis Animal Farm, Sisseln, Switzerland) are kept under sterile conditions with water and feed *ad libitum*. Tumours are induced by subcutaneous injection of cells (at least 2×10^6 cells in 100 μl phosphate-buffered saline or medium) into carrier mice (4-8 mice per tumour cell line). The resulting tumours pass through at least three consecutive transplantations before the start of treatment. Tumour fragments (about 25 mg) are implanted subcutaneously in the left flank of the animals using a 13-gauge trocar needle under Forene® anaesthesia (Abbott, Switzerland). Treatment starts when the tumours have reached a mean tumour volume of 100 mm^3. Tumour growth is determined twice and 24 hours after the last treatment by measuring the perpendicular diameter. The tumour volumes are calculated according to the formula $L \times D \times \pi/6$ (see Evans et al., Brit. J. Cancer 45, 466-8 (1982). Tumour growth is expressed as T/C% (mean increase in the tumour volume among treated animals, divided by the mean increase in tumour volume among untreated controls, multiplied by 100).

The animals are treated with a compound of formula 1 administered i.p. 7 days a week. The volumes administered are 25 ml/kg. Stock solutions of the test compounds are prepared with 4 mg/ml of test substance in 100% dimethyl sulfoxide and stirred at room temperature until a clear solution is obtained. Aliquots of the stock solution are stored at -20°C. Before administration, 10% ®Tween 80 (obtainable from Fluka, Buchs, Switzerland) is added to the stock solution, which is then diluted 1 : 100 (v/v) with sterile 0.9% physiological saline. The dilutions are prepared fresh each day before administration.

The following tumours are used as test tumours: human prostate carcinoma PC-3; see also Cancer Res. 40, 524-34 (1980) (ATCC: CRL 1435) and human non-small-cell lung carcinoma NCI-H596 (ATCC: HTB 178).

As an alternative to the said tumour cell lines, other cell lines may also be used in the same manner, for example
human epithelial cell line A-431; American Type Culture Collection (ATCC), Rockville, MD, USA, Catalogue Number ATCC CRL 1555; cell line from an 85-year-old woman; epidermoid carcinoma cell line.
- the MCF-7 breast adenocarcinoma cell line (ATCC No. HTB 22; see also J. Natl. Cancer Inst. (Bethesda) 51, 1409-16 [1973]);
- the MDA-MB 468 breast adenocarcinoma cell line (ATCC No. HTB 132; see also In Vitro 14, 911-15 [1978]);
- the MDA-MB 231 breast adenocarcinoma cell line (ATCC No. HTB 26; see also J. Natl. Cancer Inst. (Bethesda) 53, 661-74 [1974]);
- the HCT 116 colon carcinoma cell line (ATCC No. CCL 247; see also Cancer Res. 41, 1751-6 [1981]); and
- the DU145 prostate carcinoma cell line DU 145 (ATCC No. HTB 81; see also Cancer Res. 37, 4049-58 [1978]);
- the Colo 205 colon carcinoma cell line (ATCC No. CCL 222; see also Cancer Res. 38, 1345-55 [1978]); and
- the A549 lung carcinoma cell line (ATCC No. CCL 185).

On the basis of the said properties, the compounds of formula I, especially those in which R_5 stands for hydrogen, may be used preferably as tumour-inhibiting substances, for example to treat tumours of the bladder and skin. If the compounds of formula I are used for cancer therapy in combination with other chemotherapeutic agents, enhanced effects are possible. In addition, they may be considered for the further said uses as protein kinase C modulators and may especially be used for the treatment of diseases which respond to inhibition of protein kinase C.

As already indicated, compounds of formula I may be used alone or also in combination with one or more other pharmacologically active substances. A conceivable combination, for example, would be with (a) inhibitors of one or more enzymes of polyamine biosynthesis, e.g. ornithine decarboxylase or S-adenosylmethionine decarboxylase inhibitors, (b) inhibitors of tyrosine protein kinases, (c) cytokines, (d) negative growth regulators, (e) aromatase inhibitors, (f) antiestrogens, or (g) classical cytostatic or cytotoxic substances.

At concentrations in the micromolar and submicromolar range, compounds of formula I especially inhibit also certain tyrosine kinases, such as in particular the PDGF receptor and VEGF receptor kinases. In this sense, the inhibition of protein kinase C and of PDGF receptor kinase have a similar effect with regard to inhibiting cell growth.

PDGF (Platelet-derived Growth Factor) is a very commonly occurring growth factor, which plays an important role both in normal growth and also in pathological cell proliferation, such as is seen in carcinogenesis and in diseases of the smooth-muscle cells of blood vessels, for example in atherosclerosis and thrombosis. The inhibition of PDGF-stimulated receptor tyrosine kinase activity (inhibition of receptor phosphorylation) *in vitro* can be measured in PDGF receptor immune complexes of BALB/c 3T3 cells, as described by E. Andrejauskas-Buchdunger and U. Regenass in Cancer Research 52, 5353-5358 (1992).

The inhibition of PDGF-stimulated receptor tyrosine in the intact cell is detected by means of Western blot analysis, likewise as described by E. Andrejauskas-Buchdunger and U. Regenass in Cancer Research 52, 5353-5358 (1992). In this test, the inhibition of ligand-stimulated PDGF receptor autophosphorylation in BALB/c mouse cells is measured using antiphosphotyrosine antibodies. The compounds of formula I preferably inhibit the tyrosine

kinase activity of the PDGF receptor at concentrations of 0.01 to 10 μmol/litre. These compounds also inhibit the cell growth of a PDGF-dependent cell line, namely BALB/c mouse fibroblasts.

A large number of human tumours, especially gliomas and carcinomas, express high levels of VEGF ("Vascular Endothelial Growth Factor") and its receptors. Direct evidence of the role of VEGF as a tumour angiogenesis factor *in vivo* has been obtained from studies in which VEGF expression or VEGF activity was inhibited. This was achieved with antibodies which inhibit VEGF activity, with dominant-negative VEGF-R-2 mutants which inhibited signal transduction, or with the use of antisense-VEGF RNA techniques. All approaches led to a reduction in the growth of glioma cell lines or other tumour cell lines *in vivo* as a result of inhibited tumour angiogenesis.

Angiogenesis is regarded as an absolute prerequisite for those tumours which grow beyond a maximum diameter of about 1–2 mm; up to this limit, oxygen and nutrients may be supplied to the tumour cells by diffusion. Every tumour, regardless of its origin and its cause, is thus dependent on angiogenesis for its growth after it has reached a certain size.

Three principal mechanisms play an important part in the anti-tumour activity of angiogenesis inhibitors: 1) Inhibition of the growth of vessels, especially capillaries, into avascular resting tumours, with the result that there is no net tumour growth owing to the balance that is achieved between apoptosis and proliferation; 2) Prevention of the migration of tumour cells owing to the absence of bloodflow to and from tumours; and 3) Inhibition of endothelial cell proliferation, thus avoiding the paracrine growth-stimulating effect exerted on the surrounding tissue by the endothelial cells which normally line the vessels.

The efficacy of compounds of formula I as inhibitors of VEGF-receptor tyrosine kinase activity can be demonstrated as follows: test for activity against VEGF-receptor tyrosine kinase. The test is conducted using Flt-1 VEGF-receptor tyrosine kinase. The detailed procedure is as follows: 30 μl kinase solution (10 ng of the kinase domain of Flt-1, Shibuya et al., Oncogene 5, 519-24 [1990]) in 20 mM Tris•HCl pH 7.6, 5 mM manganese dichloride ($MnCl_2$), 5 mM magnesium chloride ($MgCl_2$), 1mM dithiothreitol, 10 μM Na_3VO_4 (sodium vanadate), and 30 μg/ml poly(Glu,Tyr) 4:1 (Sigma, Buchs, Switzerland), 8 μM [^{33}P]-ATP

(0.05 µCi/batch), 1% dimethyl sulfoxide, and 0 to 100 µM of the compound to be tested are incubated together for 15 minutes at room temperature. The reaction is then ended by the addition of 10 µl 0.25 M ethylenediaminetetraacetate (EDTA) pH 7. Using a multichannel dispenser (LAB SYSTEMS, USA), an aliquot of 20 µl is applied to a PVDF (= polyvinyl difluoride) Immobilon P membrane (Millipore, USA), which is incorporated into a Millipore microtitre filter manifold, and connected to a vacuum. Following complete elimination of the liquid, the membrane is washed 4 times successively in a bath containing 0.5% phosphoric acid (H_3PO_4), incubated for 10 minutes each time while shaking, then mounted in a Hewlett Packard TopCount Manifold and the radioactivity measured after the addition of 10 µl Microscint® (ß-scintillation counter liquid; Packard USA). IC_{50}-values are determined by linear regression analysis of the percentages for the inhibition of each compound in three concentrations (as a rule 0.01, 0.1, and 1 µM). IC_{50} values, for example, between 0.1 and 10 µM are measured.

On the basis of the said properties, compounds of formula I may be used not only as tumour-inhibiting substances for the treatment of a tumour disease, but also as agents to combat non-malignant proliferative disorders, such as atherosclerosis, thrombosis, psoriasis, scleroderma, and fibrosis. In addition, they may be considered for the further said uses as protein kinase C modulators and may especially be used for the treatment of diseases which respond to inhibition of PDGF receptor kinase and/or VEGF receptor kinase. In particular, combination of the anti-angiogenesis efficacy resulting from the properties of VEGF receptor kinase inhibition with the antiproliferative efficacy resulting from the properties of PKC-α inhibition may lead to an extremely high degree of antiproliferative efficacy in the sense of a synergistic effect.

The water solubility is determined as follows, for example: the compounds of formula I, or the salts thereof, are stirred with water at room temperature until no further compound dissolves (about 1 hour). The solubilities found are preferably between 0.1 and 20% by weight.

As PKC inhibitors, the staurosporine derivatives of formula I, in which R_5 has one of the said meanings with the exception of hydrogen, should be able to fully restore the sensitivity of multidrug-resistant cells to anti-tumour agents, such as cytostatics. Such anti-tumour agents

are, for example, daunorubicin, vincristine, etoposide, paclitaxel, mitomycin C, actinomycin D, mitoxantron, and especially vinblastine and doxorubicin (adriamycin). The corresponding staurosporine derivatives of formula I and pharmaceutically acceptable salts of such derivatives may therefore be used with at least one salt-forming group in combination with one or more of these anti-tumour agents for the treatment of tumour diseases.

KB-8511 tumours show an overexpression of PgP, the product of the mdr-1 gene (see S. Akiyama et al., "Isolation and genetic characterization of human KB cell lines resistant to multiple drug", Somatic Cell and Mol. Gen. 11, 117-126 [1985]).

Human KB-31 (sensitive) cells and KB-8511 (multidrug-resistant) cells (which overexpress P-glycoprotein [Pgp]) are incubated in MEM-Alpha medium, with the addition of ribonucleosides and deoxyribonucleosides and in the presence of 5% fetal calf serum, 50 units/ml of the antibiotic penicillin, and 50 µg/ml of the antibiotic streptomycin, in a 5% carbon dioxide atmosphere. The KB-8511 cells are kept as stock in in the presence of 10 ng/ml of the antineoplastic substance colcemid (demecolcine). To determine cell growth inhibition, 1500 cells each (without the addition of colcemid) are seeded in 96-well microtitre plates and incubated overnight under the said conditions. The test substance (A: the antineoplastic vinblastine, B: the compound of formula I from Example 1) is added in serial dilutions on day 1. The plates are then incubated under the said conditions for 4 days. During this time, the control cells undergo several cell divisions. After incubation, the cells are fixed with 3.3% (w/v) aqueous glutaraldehyde solution, washed with water, and stained with 0.05% (w/v) aqueous methylene blue solution. After washing, the stain is eluted with 3% (w/v) aqueous hydrochloric acid. Thereafter, the optical density (OD) per well, which is directly proportional to the number of cells, is measured using a photometer at 665 nm. The IC_{50} values are calculated with a computer system using the formula

$$[OD_{665}(test)-OD_{665}(start)]/[OD_{665}(control)-OD_{665}(start)] \times 100$$

The IC_{50} value is defined as the concentration of active substance at which the number of cells per well is reduced to 50% of the number of cells in the control culture at the end of the incubation period. The KB8511 cells also show an antiproliferative action.

In the case of the groups of radicals or compounds mentioned hereinbefore and hereinafter, general definitions may, insofar as appropriate and expedient, be replaced by the more specific definitions stated hereinbefore and hereinafter.

Preference is given to a compound of formula I wherein
R_1 and R_2 independently of each other are lower alkyl, lower alkyl substituted by halogen, C_6-C_{14}aryl, hydroxy, lower alkoxy, phenyl-lower alkoxy, phenyloxy, lower alkanoyloxy, benzoyloxy, amino, lower alkylamino, lower alkanoylamino, phenyl-lower alkylamino, N,N-di-lower alkylamino, N,N-di-(phenyl-lower alkyl)amino, cyano, mercapto, lower alkylthio, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkyl-carbamoyl, sulfo, lower alkanesulfonyl, lower alkoxysulfonyl, aminosulfonyl, N-lower - alkylaminosulfonyl or N,N-di-lower alkylaminosulfonyl; halogen; lower alkoxy; C_6-C_{14}aryloxy; C_6-C_{14}aryl-lower alkoxy; lower alkanoyloxy; C_6-C_{14}arylcarbonyloxy; amino monosubstituted or disubstituted by lower alkyl, C_6-C_{14}aryl, C_6-C_{14}aryl-lower alkyl, lower alkanoyl or C_6-C_{12}-arylcarbonyl; cyano; nitro; mercapto; lower alkylthio; C_6-C_{14}arylthio; C_6-C_{14}aryl-lower alkylthio; lower alkanoylthio; C_6-C_{14}aryl-lower alkanoylthio; carboxy; lower alkoxycarbonyl, C_6-C_{14}aryl-lower alkoxycarbonyl; C_6-C_{14}aryloxycarbonyl; carbamoyl; carbamoyl N-mono- or N,N-disubstituted by lower alkyl, C_6-C_{14}aryl or C_6-C_{14}aryl-lower alkyl; sulfo; C_6-C_{14}aryl-sulfonyl; C_6-C_{14}aryl-lower alkanesulfonyl; lower alkanesulfonyl; or aminosulfonyl N-mono- or N,N-disubstituted by lower alkyl, C_6-C_{14}aryl or C_6-C_{14}aryl-lower alkyl, wherein C_6-C_{14}aryl is an aryl radical with 6 to 12 carbon atoms in the ring system, which may be unsubstituted or substituted by halogen, phenyl or naphthyl, hydroxy, lower alkoxy, phenyl-lower alkoxy, phenyloxy, lower alkanoyloxy, benzoyloxy, amino, lower alkylamino, lower alkanoylamino, phenyl-lower alkylamino, N,N-di-lower alkylamino, N,N-di-(phenyl-lower alkyl)amino, cyano, mercapto, lower alkylthio, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkyl-carbamoyl, N,N-di-lower alkylcarbamoyl, sulfo, lower alkanesulfonyl, lower alkoxysulfonyl, aminosulfonyl, N-lower alkylaminosulfonyl or N,N-di-lower alkylaminosulfonyl;

n and m are independently of each other 0 or 1, preferably 0;

R_3 and R_4 are independently of each other
hydrogen,

lower alkyl, lower alkenyl or lower alkadienyl, which are each unsubstituted or monosubstituted or polysubsituted, preferably monosubstituted or disubstituted by a substituent independently selected from lower alkyl; hydroxy; lower alkoxy, which may be unsubstituted or mono-, di-, or trisubstituted by (i) heterocyclyl with 4 to 12 ring atoms, which may be unsaturated, wholly saturated, or partly saturated, is monocyclic or bicyclic and may contain up to three heteroatoms selected from nitrogen, oxygen and sulfur, and is most especially pyrrolyl, for example 2-pyrrolyl or 3-pyrrolyl, pyridyl, for example 2-, 3- or 4-pyridyl, or in a broader sense also thienyl, for example 2- or 3-thienyl, or furyl, for example 2-furyl, indolyl, typically 2- or 3-indolyl, quinolyl, typically 2- or 4-quinolyl, isoquinolyl, typically 3- or 5-isoquinolyl, benzofuranyl, typically 2-benzofuranyl, chromenyl, typically 3-chromenyl, benzothienyl, typically 2- or 3-benzothienyl; imidazolyl, typically 1- or 2-imidazolyl, pyrimidinyl, typically 2-or 4-pyrimidinyl, oxazolyl, typically 2-oxazolyl, isoxazolyl, typically 3-isoxazolyl, thiazolyl, typically 2-thiazolyl, benzimidazolyl, typically 2-benzimidazolyl, benzoxazolyl, typically 2-benzoxazolyl, quinazolyl, typically 2-quinazolinyl, 2-tetrahydrofuryl, 4-tetrahydrofuryl, 4-tetrahydropyranyl, 1-, 2- or 3-pyrrolidyl, 1-, 2-, 3-, or 4-piperidyl, 1-, 2-or 3-morpholinyl, 2- or 3-thiomorpholinyl, 2-piperazinyl or N,N'-bis-lower alkyl-2-piperazinyl, (ii) by halogen, (iii) by hydroxy or (iv) by lower alkoxy; phenoxy; phenyl-lower alkoxy; heterocyclyloxy, wherein heterocyclyl is pyrrolyl, for example 2-pyrrolyl or 3-pyrrolyl, pyridyl, for example 2-, 3- or 4-pyridyl, or in a broader sense also thienyl, for example 2- or 3-thienyl, or furyl, for example 2-furyl, indolyl, typically 2- or 3-indolyl, quinolyl, typically 2- or 4-quinolyl, isoquinolyl, typically 3- or 5-isoquinolyl, benzofuranyl, typically 2-benzofuranyl, chromenyl, typically 3-chromenyl, benzothienyl, typically 2- or 3-benzothienyl; imidazolyl, typically 1- or 2-imidazolyl, pyrimidinyl, typically 2-or 4-pyrimidinyl, oxazolyl, typically 2-oxazolyl, isoxazolyl, typically 3-isoxazolyl, thiazolyl, typically 2-thiazolyl, benzimidazolyl, typically 2-benzimidazolyl, benzoxazolyl, typically 2-benzoxazolyl, quinazolyl, typically 2-quinazolinyl, 2-tetrahydrofuryl, 4-tetrahydrofuryl, 2- or 4-tetrahydropyranyl, 1-, 2- or 3-pyrrolidyl, 1-, 2-, 3-, or 4-piperidyl, 1-, 2-or 3-morpholinyl, 2- or 3-thiomorpholinyl, 2-piperazinyl or N,N'-bis-lower alkyl-2-piperazinyl, such as especially 2- or 4-tetrahydropyranyloxy; lower alkanoyloxy; carboxy; lower alkoxycarbonyl; phenyl-lower alkoxycarbonyl; mercapto; lower alkylthio; phenylthio; halogen; halogen-lower alkyl; oxo (except in the 1-position, because otherwise acyl); azido; nitro; cyano; amino; mono-lower alkylamino; di-lower alkylamino; pyrrolidino; imidazol-1-yl; piperidino; piperazino; 4-lower alkylpiperazino; morpholino; thiomorpholino; diphenylamino or dibenzylamino unsubstituted

or substituted in the phenyl part by lower alkyl, lower alkoxy, halogen and/or nitro; lower alkoxycarbonylamino; phenyl-lower alkoxycarbonylamino unsubstituted or substituted in the phenyl part by lower alkyl or lower alkoxy; fluorenylmethoxycarbonylamino; amino-lower alkyl; monosubstituted or disubstituted amino-lower alkyl, wherein the amino substituent is selected from lower alkyl, hydroxy-lower alkyl, C_3-C_8cycloalkyl, amino-lower alkyl, N-mono- or N,N-di(-lower alkyl)amino-lower alkyl, amino, N-mono- or N,N-di-lower alkylamino and N-mono- or N,N-di-(hydroxy-lower alkyl)amino; pyrrolidino-lower alkyl; piperidino-lower alkyl; piperazino-lower alkyl; 4-lower alkylpiperazino-lower alkyl; imidazol-1-yl-lower alkyl; morpholino-lower alkyl; thiomorpholino-lower alkyl; S-oxo-thiomorpholino-lower alkyl; S,S-dioxothiomorpholino-lower alkyl; lower alkylendioxy; sulfamoyl; sulfo; carbamoyl; ureido; guanidino; cyano; aminocarbonyl (carbamoyl), which is substituted by one or two radicals on the nitrogen, wherein the amino substituents are selected independently of one another from the group comprising lower alkyl, hydroxy-lower alkyl, C_3-C_8cycloalkyl, amino-lower alkyl, N-mono- or N,N-di(-lower alkyl)amino-lower alkyl, amino, N-mono- or N,N-di-lower alkylamino and N-mono- or N,N-di-(hydroxy-lower alkyl)amino; pyrrolidinocarbonyl; piperidinocarbonyl; piperazinocarbonyl; 4-lower alkylpiperazinocarbonyl; imidazolinocarbonyl; morpholinocarbonyl; thiomorpholinocarbonyl; S-oxo-thiomorpholinocarbonyl; and S,S-dioxothiomorpholino;

phenyl, naphthyl, phenyl-lower alkyl or phenyl-lower alkenyl with a terminal phenyl radical, which is unsubstituted or monosubstituted or disubstituted by the radicals named above as substituents of lower alkyl, lower alkenyl or lower alkadienyl;

or heterocyclyl-lower alkyl, wherein heterocyclyl is pyrrolyl, for example 2-pyrrolyl or 3-pyrrolyl, pyridyl, for example 2-, 3- or 4-pyridyl, or in a broader sense also thienyl, for example 2- or 3-thienyl, or furyl, for example 2-furyl, indolyl, typically 2- or 3-indolyl, quinolyl, typically 2- or 4-quinolyl, isoquinolyl, typically 3- or 5-isoquinolyl, benzofuranyl, typically 2-benzofuranyl, chromenyl, typically 3-chromenyl, benzothienyl, typically 2- or 3-benzothienyl; imidazolyl, typically 1- or 2-imidazolyl, pyrimidinyl, typically 2-or 4-pyrimidinyl, oxazolyl, typically 2-oxazolyl, isoxazolyl, typically 3-isoxazolyl, thiazolyl, typically 2-thiazolyl, benzimidazolyl, typically 2-benzimidazolyl, benzoxazolyl, typically 2-benzoxazolyl, quinazolyl, typically 2-quinazolinyl, 2-tetrahydrofuryl, 4-tetrahydrofuryl, 2- or 4-tetrahydropyranyl, 1-, 2- or 3-pyrrolidyl, 1-, 2-, 3-, or 4-piperidyl, 1-, 2-or 3-morpholinyl, 2- or

3-thiomorpholinyl, 2-piperazinyl or N,N'-bis-lower alkyl-2-piperazinyl, which in each case are unsubstituted or monosubstituted or disubstituted by the radicals named above as substituents of lower alkyl, lower alkenyl, or lower alkadienyl;
whereby R_4 may also be absent:

or
R_4 is absent, and

R_3 is acyl of the subformulae Y-C(=W)-, wherein W is oxygen and Y is hydrogen, R°, R°-O-, R°HN-, or R°R°N- (wherein the radicals R° may be the same or different),

or
is acyl of the subformula R°-SO_2-,

wherein R° in the said radicals has the following meanings: lower alkyl, especially methyl or ethyl, amino-lower alkyl, wherein the amino group is unprotected or is protected by a conventional amino protecting group – especially by lower alkoxycarbonyl, typically tert-lower alkoxycarbonyl, for example tert-butoxycarbonyl – e.g. aminomethyl, R,S-, R- or preferably S-1-aminoethyl, tert-butoxycarbonylaminomethyl or R,S-, R-, or preferably S-1-(tert-butoxycarbonylamino)ethyl, carboxy-lower alkyl, typically 2-carboxyethyl, lower alkoxycarbonyl-lower alkyl, typically 2-(tert-butoxycarbonyl)ethyl, cyano-lower alkyl, typically 2-cyanoethyl, tetrahydropyranyloxy-lower alkyl, typically 4-(tetrahydropyranyl)oxymethyl, morpholino-lower alkyl, typically 2-(morpholino)ethyl, phenyl, lower alkylphenyl, typically 4-methylphenyl, lower alkoxyphenyl, typically 4-methoxyphenyl, imidazolyl-lower alkoxyphenyl, typically 4-[2-(imidazol-1-yl)ethyl)oxyphenyl, carboxyphenyl, typically 4-carboxyphenyl, lower alkoxycarbonylphenyl, typically 4-ethoxycarbonylphenyl or 4-methoxyphenyl, halogen-lower alkylphenyl, typically 4-chloromethylphenyl, pyrrolidino-phenyl, typically 4-pyrrolidinophenyl, imidazol-1-ylphenyl, typically 4-(imidazolyl-1-yl)phenyl, piperazinophenyl, typically 4-piperazinophenyl, (4-lower alkylpiperazino)phenyl, typically 4-(4-methylpiperazino)phenyl, morpholinophenyl, typically 4-morpholinophenyl, pyrrolidino-lower alkylphenyl, typically 4-pyrrolidinomethylphenyl, imidazol-1-yl-lower alkylphenyl, typically 4-(imidazolyl-1-ylmethyl)phenyl, piperazino-lower alkylphenyl, typically 4-piper-azinomethylphenyl, (4-lower alkylpiperazinomethyl)-phenyl, typically 4-(4-methylpiper-

azinomethyl)phenyl, morpholino-lower alkylphenyl, typically 4-morpholinomethylphenyl, piperazinocarbonylphenyl, typically 4-piperazinocarbonylphenyl, or (4-lower alkylpiperazino)phenyl, typically 4-(4-methylpiperazino)phenyl.

p is 0 if R_4 is absent, or is 1 if R_3 and R_4 are both present and in each case are one of the aforementioned radicals;

R_5 is hydrogen or lower alkyl, especially hydrogen,

X stands for 2 hydrogen atoms, for O, or for 1 hydrogen atom and hydroxy; or for 1 hydrogen atom and lower alkoxy;

Z is hydrogen or especially lower alkyl, most especially methyl;

and either the two bonds characterised by wavy lines are preferably absent in ring A and replaced by 4 hydrogen atoms, and the two wavy lines in ring B each, together with the respective parallel bond, signify a double bond;

or also the two bonds characterised by wavy lines are absent in ring B and replaced by a total of 4 hydrogen atoms, and the two wavy lines in ring A each, together with the respective parallel bond, signify a double bond;

or both in ring A and in ring B all of the 4 wavy bonds are absent and are replaced by a total of 8 hydrogen atoms;

or a salt thereof, if at least one salt-forming group is present.

Particular preference is given to a compound of formula I wherein

m and n are each 0;

R_3 and R_4 are independently of each other

hydrogen,

lower alkyl unsubstituted or mono- or disubstituted, especially monosubstituted, by radicals selected independently of one another from carboxy; lower alkoxycarbonyl; and cyano; whereby R_4 may also be absent;

or
R_4 is absent, and

R_3 is acyl from the subformula R°-CO, wherein R° is lower alkyl, especially methyl or ethyl; amino-lower alkyl, wherein the amino group is unprotected or protected by lower alkoxycarbonyl, typically tert-lower alkoxycarbonyl, for example tert-butoxycarbonyl, e.g. aminomethyl, R,S-, R-, or preferably S-1-aminoethyl, tert-butoxycarbonylaminomethyl or R,S-, R-, or preferably S-1-(tert-butoxycarbonylamino)ethyl; tetrahydropyranyloxy-lower alkyl, typically 4-(tetrahydropyranyl)oxymethyl; phenyl; imidazolyl-lower alkoxyphenyl, typically 4-[2-(imidazol-1-yl)ethyl)oyxphenyl; carboxyphenyl, typically 4-carboxyphenyl; lower alkoxycarbonylphenyl, typically 4-methoxy- or 4-ethoxycarbonylphenyl; halogen-lower alkylphenyl, typically 4-chloromethylphenyl; imidazol-1-ylphenyl, typically 4-(imidazolyl-1-yl)-phenyl; pyrrolidino-lower alkylphenyl, typically 4-pyrrolidinomethylphenyl; piperazino-lower alkylphenyl, typically 4-piperazinomethylphenyl; (4-lower alkylpiperazinomethyl)phenyl, typically 4-(4-methylpiperazinomethyl)phenyl; morpholino-lower alkylphenyl, typically 4-morpholinomethylphenyl; piperazinocarbonylphenyl, typically 4-piperazinocarbonylphenyl; or (4-lower alkylpiperazino)phenyl, typically 4-(4-methylpiperazino)phenyl;

or is acyl of the subformula R°-O-CO-, wherein R° is lower alkyl;

or is acyl of the subformula R°HN-C(=W)-, wherein W is oxygen and R° has the following preferred meanings: morpholino-lower alkyl, typically 2-morpholinoethyl, phenyl, lower alkoxyphenyl, typically 4-methoxyphenyl or 4-ethoxyphenyl, carboxyphenyl, typically 4-carboxyphenyl, or lower alkoxycarbonylphenyl, typically 4-ethoxycarbonylphenyl;

or is lower alkylphenylsulfonyl, typically 4-toluenesulfonyl;

p is 0 if R_4 is absent, or is 1 if R_3 and R_4 are both present and in each case are one of the aforementioned radicals;

R_5 is hydrogen or lower alkyl, especially hydrogen,

X stands for 2 hydrogen atoms or for O;

Z is methyl;

and either the two bonds characterised by wavy lines are preferably absent in ring A and replaced by 4 hydrogen atoms, and the two wavy lines in ring B each, together with the respective parallel bond, signify a double bond;

or also the two bonds characterised by wavy lines are absent in ring B and replaced by a total of 4 hydrogen atoms, and the two wavy lines in ring A each, together with the respective parallel bond, signify a double bond;

or both in ring A and in ring B all of the 4 wavy bonds are absent and are replaced by a total of 8 hydrogen atoms;

or a salt thereof, if at least one salt-forming group is present.

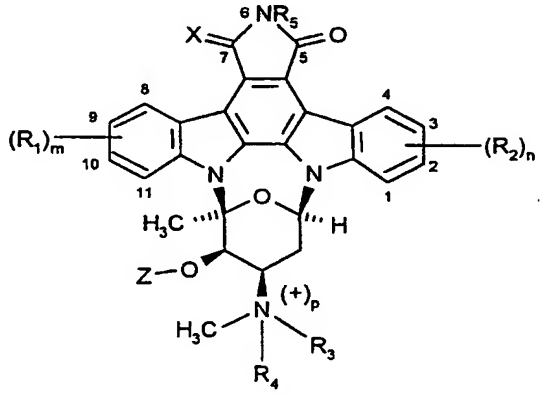
Especially preferred are the compounds of formula I named in the Examples, or their salts, especially the pharmaceutically acceptable salts thereof.

Most especially preferred is the compound of formula I designated 1,2,3,4-tetrahydro-staurosporine, or a (particularly pharmaceutically acceptable) salt thereof (here, m und n in formula I are 0, R_3 is hydrogen, R_4 is absent, provided no salt is present (p = 0), or is hydrogen if a salt is present (p = 1), R_5 is hydrogen, the two bonds represented by wavy lines are absent in Ring A and are replaced by a total of 4 hydrogen atoms and the two bonds represented by wavy lines in Ring B are in each case a double bond together with the parallel bonds, X stands for 2 hydrogen atoms, and Z is methyl).

Preparation process

The compounds of formula I may be prepared by methods known *per se*, preferably by

a) hydrogenating a compound of formula III,



(III)

wherein R_1, R_2, R_3, R_4, R_5, n, m, p, X and Z are as defined for compounds of formula I, or

b) for the preparation of a compound of formula I, wherein R_1, R_2, R_5, n, m, p, X, Z and the wavy lines in rings A and B are as defined for a compound of formula I, R_3 and R_4 are independently of one another one of the radicals named under formula I subject to the proviso that at least one of the radicals is different from hydrogen, whereby R_4 may also be absent, reacting a compound of formula I, wherein R_3 is hydrogen and the meanings of the other symbols are as defined for a compound of formula I, with a compound of formula IV,

$$R_{3,4}\text{-}L \qquad (IV)$$

wherein $R_{3,4}$ has the meaning as defined for R_3 or R_4 under compounds of formula I, with the exception of hydrogen, and L stands for hydroxy or a nucleofugal leaving group, or

c) for the preparation of a compound of formula I, wherein R_1, R_2, R_5, n, m, p, X, Z and the wavy lines in rings A and B are as defined for compounds of formula I, R_4 is hydrogen or is absent, and R_3 is a radical of the subformula Y-C(=W)-, wherein W is oxygen or sulfur and Y is an amino group or a substituted amino group, carbamoylating a compound of formula I,

wherein R_3 is hydrogen, R_4 is hydrogen or is absent, and the meanings of the other symbols are as defined for a compound of formula I, with a compound of formula V,

$$Y=C(=W) \qquad (V)$$

wherein Y is an amino group or a substituted amino group and W is oxygen or sulfur, or

d) for the preparation of a compound of formula I, wherein R_1, R_2, R_5, n, m, p, X, Z and the wavy lines in rings A and B are as defined for compounds of formula I, R_3 is one of the radicals named under formula I with the exception of hydrogen and acyl, and R_4 is hydrogen or is absent, adding a compound of formula I, wherein R_3 is hydrogen, R_4 is hydrogen or is absent, and the meanings of the other symbols are as defined for a compound of formula I, to a compound of formula VI,

$$R_3^* \qquad (VI)$$

which corresponds to the radical R_3 that is to be introduced, but differs insofar as it contains a double bond instead of a hydrogen atom and the bond to the radical of the molecule in formula I, or

e) for the preparation of a compound of formula I, wherein R_1, R_2, n, m, p, X, Z and wavy lines in rings A and B are as defined for a compound of formula I, R_4 is absent or is hydrogen, and R_3 and R_5 are identical to radicals named under formula I, although R_3 is not selected from acyl or hydrogen and R_5 is not selected from hydrogen, reductively alkylating a compound of formula I, wherein R_3 and R_5 are each hydrogen and the other symbols have the last-named meanings, with an aldehyde or ketone of formula VII,

$$R_{3,5}^{**} \qquad (VII)$$

which corresponds to the radicals R_3 and R_5 that are to be introduced, but differs insofar as it contains a carbonyl group instead of the bonding methylene or methylidene group,

and, if so desired, converting an obtainable compound of formula I to a different compound of formula I; converting an obtainable free compound of formula I into a corresponding salt; converting a corresponding salt of a compound of formula I into the free compound or another salt of the corresponding compound of formula I; and/or separating an isomeric mixture into the individual isomers;

in reaction variants a), b), c), d), and e) and the conversions in the starting compounds, free functional groups which should not take part in the reaction are present in protected form, if necessary, and any protecting groups are removed after the reaction; and educts may exist in free form or in salt form, if a salt-forming group is present.

Detailed description of the preferred process variants

Unless otherwise indicated, the symbols R_1, R_2, R_3, R_4, R_5, n, m, p, X, Z and the wavy lines in rings A and B, as used in the following detailed description of the process steps and the additional process steps, have the meanings as defined for compounds of formula I.

Process a): Hydrogenation

The hydrogenation of a compound of formula I under partial reduction of ring A and/or ring B is carried out primarily by catalytic hydrogenation, preferably using a precious metal catalyst, such as platinum or rhodium, which may be bound to a substrate, such as activated charcoal, aluminium oxide or barium sulfate, under normal pressure or preferably elevated hydrogen pressure, especially between 3 and 300 bar, preferably between 20 and 120 bar, in suitable solvents, such as alcohols, for example butanol, or ethers, for example tetrahydrofuran, or mixtures of such solvents, preferably at elevated temperatures, preferably at temperatures between 40 and 150°C, especially between 60 and 135°C.

Starting from a compound of formula III, wherein m and n are 0, R_3 is hydrogen, R_4 is absent, p is 0, X stands for 2 hydrogen atoms, and Z is methyl (staurosporine), this reaction serves as a means of preparing 1,2,3,4-tetrahydrostaurosporine, 8,9,10,11-tetrahydro-staurosporine, or 1,2,3,4,8,9,10,11-octahydrostaurosporine.

Depending on reaction conditions, only one or both of the rings A and B may be partially hydrogenated; for example, using rhodium catalysts on a substrate at relatively high

pressures and temperatures a hydrogenation of both rings is achieved, whereas using palladium on a substrate at pressures and temperatures that are not so high only one of the two rings is reduced per molecule.

Process b): Alkylation or acylation

A nucleofugal leaving group L in a compound of formula IV is preferably halogen, such as especially chlorine, bromine or iodine (the corresponding compound is then a halogenide or an acid halide), but may also be another hydroxy group esterified with a strong inorganic or organic acid, typically with another strong organic sulfonic acid, typically hydroxy esterified with a lower alkanesulfonic acid substituted if need be, for example, by halogen, typically fluorine, or an aromatic sulfonic acid, for example a benzenesulfonic acid which is unsubstituted or substituted by lower alkyl, typically methyl, halogen, typically bromine, and/or nitro, for example a methanesulfonic acid, p-bromotoluenesulfonic acid or p-toluenesulfonic acid, or hydroxy esterified with hydrazoic acid, or the radical L is a radical $R_{3,4}$-O-, wherein the radical $R_{3,4}$ has the same meanings as those indicated under formula IV, so that the compound of formula IV is a symmetrical anhydride. If $R_{3,4}$ is acyl bonded via carboxy, the nucleofugal leaving group L may also form an activated ester with the adjacent carbonyl group, for example a nitrophenyl ester, typically 4-nitrophenyl ester (then L is equivalent to nitrophenyloxy); a simple phenyl ester is also possible (L = phenoxy).

When using educts of formula IV with such nucleofugal leaving groups, the reaction takes place in the presence or absence of bases, especially tertiary organic nitrogenous bases, such as tri-lower alkylamines, for example N-ethyl diisopropylamine. The reaction is carried out preferably in suitable solvents or also, if the compound of formula IV is liquid under the reaction conditions, without solvents. Suitable solvents are especially chlorinated hydrocarbons, such as chloroform or methylene chloride, and carboxamides, such as dimethylformamide. Preferred reaction temperatures lie between 0 and 120°C, especially between about 20°C and the reflux temperature or up to 100°C.

It is also possible to prepare a nucleophilic leaving group from a hydroxy group *in situ*, for example by adding coupling reagents, such as N-(3-dimethylaminopropyl)-N'-ethyl-carbodiimide salts, typically the hydrochloride, in the presence of 1-hydroxybenzotriazole, or diethylcyanophosphonate, N,N'-dicyclohexylcarbodiimide in the presence or absence of 1-

hydroxybenzotriazole, the solvents, temperatures etc. being the same as those mentioned in the last paragraph.

Process c): Carbamoylation

A compound of formula V is an isocyanate (W = oxygen) or an isothiocyanate (W = sulfur).

The reaction preferably takes place in suitable solvents, such as chlorinated hydrocarbons, for example in chloroform or methylene chloride, at temperatures between 0°C and the reflux temperature of the respective reaction mixture, especially between 15 and 55°C, in the presence or absence of an inert gas such as nitrogen or argon.

Process d): Addition to a double bond

A compound of formula VI which corresponds to the radical R_3 to be introduced, but differs from it insofar as it contains a double bond instead of a hydrogen atom and the bond to the radical of the molecule in formula I, is for example a cyano-lower alkene compound, such as acrylonitrile, which is suitable for the introduction of a cyano-lower alkyl radical R_3, typically 2-cyanoethyl, or a lower alkene-carbonic acid-lower alkyl ester, such as tert-butyl acrylate, which is suitable for the introduction of a lower alkoxycarbonyl-lower alkyl radical R_3, such as 2-tert-butoxycarbonylethyl.

The reaction takes place at elevated temperature, preferably between 100 and 150°C, especially in a sealed tube, in the presence of, or preferably in the absence of, an inert solvent or solvent mixture.

Process e): Reductive alkylation

An aldehyde or ketone of formula VII which corresponds to the radical R_3 and R_5 to be introduced, but differs from it insofar as it contains a carbonyl group instead of the bonding methylene or methylidene group, may also be present in reactively modified form, for example as a bisulfite adduct or especially a hemiacetal or ketal of the compounds of formula VII with alcohols, for example lower alkanols. Preferred are the free aldehydes of formula VII, especially lower alkane aldehydes, typically formaldehyde, which are suitable for the introduction of lower alkyl, such as methyl, R_3 and R_5.

Reductive alkylation takes place preferably under hydrogenation in the presence of a catalyst, especially a precious-metal catalyst, typically platinum or especially palladium, which is preferably bound to a carrier, such as carbon, or in the presence of a heavy-metal catalyst, typically Raney-Nickel, at normal pressure or at pressures from 0.1 to 10 megapascal (MPa), or under reduction using complex hydrides, typically boranes, especially alkali metal cyanoborohydride, for example sodium cyanoborohydride, in the presence of a suitable acid, preferably a relatively weak acid, typically a lower alkanecarboxylic acid, especially acetic acid, or a sulfonic acid, such as p-toluenesulfonic acid; in customary solvents, for example alcohols, such as methanol or ethanol, or lower alkylcyanides, such as acetonitrile, in the presence or absence of water.

Additional process steps

a) Conversion of compounds of formula I to other compounds of formula I:
The reactions take place according to methods known *per se*. Preferred reactions and the appropriate reaction conditions are defined in the Examples.

Further additional processes concern salt conversions and isomer separation.

Salts of a compound of formula I with at least one salt-forming group may be prepared in a manner known *per se*.

Salts may also be converted to free compounds in the customary manner, metal and ammonium salts for example by treatment with suitable acids, and acid addition salts for example by treatment with a suitable basic agent. The conversion of a compound of formula I to another salt may take place via the free compounds of formula I thus prepared, or directly through reaction of a salt as described above for the preparation of salts from free compounds of formula I.

Stereoisomeric mixtures, i.e. mixtures of diastereomers and/or enantiomers, such as racemic mixtures for example, can be separated into their corresponding isomers in a manner known *per se* by means of suitable separation methods. Diastereomeric mixtures

for example may be separated into their individual diastereomers by means of fractionated crystallization, chromatography, solvent distribution, etc. Enantiomeric mixtures, such as racemates, can be separated from one another after converting the optical antipodes to diastereomers, for example with optically active compounds, e.g. optically active acids or bases, by means of chromatography on acid materials coated with optically active compounds or by enzymatic methods, for example through selective reaction of only one of the two enantiomers. This separation may take place either at the level of one of the starting compounds or with a compound of formula I itself.

Protecting groups, their introduction and removal

In the reaction variants a), b), c), d), and e) and in the transformation processes, as well as in precursor steps prior to the preparation of educts, free functional groups, which should not take part in the reaction, may be present in the starting compounds, if necessary in protected form, and the protecting groups are then removed after the reaction concerned, or at a suitable stage of the reaction.

If one or more other functional groups, for example carboxy, hydroxy, amino, or mercapto, are or need to be protected, because they should not take part in the reaction, these are such as are usually used in the synthesis of peptide compounds, and also of cephalosporins and penicillins, as well as nucleic acid derivatives and sugars. The protecting groups may already be present in precursors and should protect the functional groups concerned against unwanted secondary reactions, such as acylations, etherifications, esterifications, oxidations, solvolysis, and similar reactions. In certain cases, the protecting groups may, in addition to this protection, effect a selective, typically stereoselective, course of reactions. It is characteristic of protecting groups that they lend themselves readily, i.e. without any unwanted secondary reactions, to removal, typically by solvolysis, photolysis, or also by enzyme activity, for example also under physiological conditions; or also by reduction, although functional groups may then have to be introduced again for further reactions after one of the reduction and/or hydrogenation processes mentioned hereinabove and hereinafter. The specialist knows, or can easily establish, which protecting groups are suitable with the reactions mentioned hereinabove and hereinafter.

The protection of functional groups by such protecting groups, the protecting groups themselves, and their cleavage reactions are described for example in standard reference works, such as J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London and New York 1973, in T. W. Greene, "Protective Groups in Organic Synthesis", Wiley, New York 1981, in "The Peptides"; Volume 3 (editors: E. Gross and J. Meienhofer), Academic Press, London and New York 1981, in "Methoden der organischen Chemie" (*Methods of organic chemistry*), Houben Weyl, 4th edition, Volume 15/I, Georg Thieme Verlag, Stuttgart 1974, in H.-D. Jakubke and H. Jescheit, "Aminosäuren, Peptide, Proteine" (*Amino acids, peptides, proteins*), Verlag Chemie, Weinheim, Deerfield Beach, and Basel 1982, and in Jochen Lehmann, "Chemie der Kohlenhydrate: Monosaccharide und Derivate" (*Chemistry of carbohydrates: monosaccharides and derivatives*), Georg Thieme Verlag, Stuttgart 1974.

The removal of protecting groups, which are not an integral part of the desired end-product of formula I or of intermediate compounds, is carried out using methods known *per se*. The removal of protecting groups, for example, is described in the standard reference works cited hereinabove in the section on "Protecting groups", or corresponds to the methods shown in the Examples.

In the additional process steps, carried out as desired, functional groups of the starting compounds which should not take part in the reaction may be present in unprotected form or may be protected for example by one or more of the protecting groups mentioned hereinabove. The protecting groups are then wholly or partly removed according to one of the standard methods as described for example in the reference works cited hereinabove.

Educts may, if a salt-forming group is present, exist in free form or also in salt form (= as a salt), provided the latter does not hinder the reaction.

General process conditions

All process steps described here can be carried out under known reaction conditions, preferably under those specifically mentioned, in the absence of or usually in the presence of solvents or diluents, preferably such as are inert to the reagents used and able to dissolve these, in the absence or presence of catalysts, condensing agents or neutralisiing

agents, for example ion exchangers, typically cation exchangers, for example in the H^+ form, depending on the type of reaction and/or reactants at reduced, normal, or elevated temperature, for example in the range from -100°C to about 190°C, preferably from about -80°C to about 150°C, for example at -80 to -60°C, at room temperature, at - 20 to 40°C or at the boiling point of the solvent used, under atmospheric pressure or in a closed vessel, if need be under pressure, and/or in an inert, for example an argon or nitrogen, atmosphere.

Salts may be present in all starting compounds and intermediates, if these contain salt-forming groups. Salts may also be present during the reaction of such compounds, provided the reaction is not thereby disturbed.

In certain cases, for example in hydrogenation, it is possible to achieve stereoselective reactions.

The solvents from which those can be selected which are suitable for the reaction in question include for example water, esters, typically lower alkyl-lower alkanoate, e.g diethyl acetate, ethers, typically aliphatic ethers, e.g. diethylether, or cyclic ethers, e.g. tetrahydrofuran, liquid aromatic hydrocarbons, typically benzene or toluene, alcohols, typically methanol, ethanol or 1- or 2-propanol, nitriles, typically acetonitrile, halogenated hydrocarbons, typically methylene chloride, acid amides, typically dimethylformamide, bases, typically heterocyclic nitrogenous bases, e.g. pyridine, carboxylic acid anhydrides, typically lower alkane acid anhydrides, e.g. acetic anhydride, cyclic, linear, or branched hydrocarbons, typically cyclohexane, hexane, or isopentane, or mixtures of these solvents, e.g. aqueous solutions, unless otherwise stated in the description of the process. Such solvent mixtures may also be used in processing, for example through chromatography or distribution.

The invention relates also to those forms of the process in which one starts from a compound obtainable at any stage as an intermediate and carries out the missing steps, or breaks off the process at any stage, or forms a starting material under the reaction conditions, or uses said starting material in the form of a reactive derivative or salt, or produces a compound obtainable by means of the process according to the invention and processes the said compound *in situ*. In the preferred embodiment, one starts from those

starting materials which lead to the compounds described hereinabove as preferred, particularly as especially preferred, primarily preferred, and/or preferred above all.

At all suitable stages, protecting groups may be found, as described hereinabove. The nature of the protecting groups, their introduction, and their removal may be as described hereinabove.

In the preferred embodiment, a compound of formula I is prepared according to the processes and process steps defined in the Examples.

Pharmaceutical preparations, methods, and uses

The invention concerns also the use of compounds of formula I, preferably in the form of pharmaceutical compositions, for the therapeutic treatment of the animal or in particular the human body, especially in the case of said diseases, or the use of these compounds for the preparation of pharmaceutical preparations for the treatment of corresponding diseases. The invention relates also to a method for the treatment of one of the said diseases, especially by inhibition of protein kinase C, PDGF-receptor tyrosine kinase, and/or VEGF-receptor tyrosine kinase, in a warm-blooded animal requiring such treatment, wherein a compound of formula I (wherein R_5 is preferably hydrogen) is administered to this warm-blooded animal in a dose which effectively inhibits protein kinase C, PDGF-receptor tyrosine kinase, and cdc2- and/or VEGF-receptor tyrosine kinase. The invention relates also to a method for the treatment of a tumour disease in combination with a cytostatic agent, such as adriamycin, and also tumour diseases resistant to the cytostatic itself, in a warm-blooded animal requiring such treatment, wherein a compound of formula I (wherein R_5 is preferably hydrogen) is administered in a dose capable of lowering or abolishing multidrug resistance.

The dose of the active substance is dependent on, amongst other factors, the nature of the disease, the nature and size of the species to be treated, the immune status of the body, and the mode of administration. For example, a daily dose of 1 mg to 3500 mg, mostly of 100 mg to 2500 mg, preferably of 200 mg to 800 mg, for example 500 mg, of a compound of formula I is administered to a warm-blooded animal of about 70 kg bodyweight. This total daily dosage is preferably given in 1–3 daily doses. The dosage in oral administration is

about two to three times higher than in parenteral administration, and thus in the upper range of the doses indicated.

The invention relates also to pharmaceutical preparations which contain an effective amount of active substance, especially an effective amount for prevention or treatment of one of the said diseases, together with pharmaceutically acceptable carriers which are suitable for topical, enteral, for example oral or rectal, or parenteral administration and may be inorganic or organic and solid or liquid.

The pharmaceutical compositions comprise preferably from about 1% to about 95% active ingredient, single-dose administration forms comprising in the preferred embodiment from about 20% to about 90% active ingredient and forms that are not of single-dose type comprising in the preferred embodiment from about 5% to about 20% active ingredient. Lyophilisates may contain up to 100% of the active substance or substances. An active substance concentration of less than 1% is especially suitable for preparations for topical application.

Unit dose forms are, for example, coated and uncoated tablets, ampoules, vials, suppositories, or capsules. Examples are capsules containing from about 0.05 g to about 1.0 g of active substance.

The present pharmaceutical compositions are prepared in a manner known *per se*, for example by means of conventional mixing, granulating, coating, dissolving or lyophilising processes.

Preference is given to the use of solutions of the active ingredient, and also suspensions or dispersions, especially isotonic aqueous solutions, dispersions or suspensions which, for example in the case of lyophilised compositions which comprise the active ingredient on its own or together with a carrier, for example mannitol, can be made up before use. The pharmaceutical compositions may be sterilised and/or may comprise excipients, for example preservatives, stabilisers, wetting agents and/or emulsifiers, solubilisers, salts for regulating the osmotic pressure and/or buffers and are prepared in a manner known *per se*, for example by means of conventional dissolving and lyophilising processes. The said solutions

or suspensions may comprise viscosity-increasing agents, typically sodium carboxymethylcellulose, carboxymethylcellulose, dextran, polyvinylpyrrolidone, or gelatins, or also solubilizers, for example ®Tween 80 [polyoxyethylen(20)sorbitan mono-oleate; trademark of ICI Americas, Inc, USA].

Suspensions in oil comprise as the oil component the vegetable, synthetic, or semi-synthetic oils customary for injection purposes. In respect of such, special mention may be made of liquid fatty acid esters that contain as the acid component a long-chained fatty acid having from 8 to 22, especially from 12 to 22, carbon atoms, for example lauric acid, tridecylic acid, myristic acid, pentadecylic acid, palmitic acid, margaric acid, stearic acid, arachidic acid, behenic acid or corresponding unsaturated acids, for example oleic acid, elaidic acid, erucic acid, brassidic acid or linoleic acid, if desired with the addition of antioxidants, for example vitamin E, β-carotene or 3,5-di-tert-butyl-4-hydroxytoluene. The alcohol component of those fatty acid esters has a maximum of 6 carbon atoms and is a mono- or polyhydric, for example a mono-, di- or trihydric, alcohol, for example methanol, ethanol, propanol, butanol or pentanol or the isomers thereof, but especially glycol and glycerol. As fatty acid esters, therefore, the following are mentioned: thyl oleate, isopropyl myristate, isopropyl palmitate, "Labrafil M 2375" (polyoxyethylene glycerol trioleate from Gattefossé, Paris), "Labrafil M 1944 CS" (unsaturated polyglycolised glycerides prepared by alcoholysis of apricot seed oil and consisting of glycerides and polyethylene glycol ester; Gattefossé, France), "Labrasol" (saturated polyglycolized glycerides prepared by alcoholysis of TCM and consisting of glycerides and polyethylene glycol ester; Gattefossé, Frankreich), and/or "Miglyol 812" (triglyceride of saturated fatty acids of chain length C_8 to C_{12} from Hüls AG, Germany), but especially vegetable oils such as cottonseed oil, almond oil, olive oil, castor oil, sesame oil, soybean oil and more especially groundnut oil.

The manufacture of injectable preparations is usually carried out under sterile conditions, as is the filling, for example, into ampoules or vials, and the sealing of the containers.

Pharmaceutical compositions for oral administration can be obtained, for example, by combining the active ingredient with one or more solid carriers, if need be granulating a resulting mixture, and processing the mixture or granules, if desired, to form tablets or tablet cores, if need be by the inclusion of additional excipients.

Suitable carriers are especially fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations, and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, and also binders, such as starches, for example corn, wheat, rice or potato starch, methylcellulose, hydroxypropyl methylcellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone, and/or, if desired, disintegrators, such as the above-mentioned starches, also carboxymethyl starch, crosslinked polyvinylpyrrolidone, alginic acid or a salt thereof, such as sodium alginate. Additional excipients are especially flow conditioners and lubricants, for example silicic acid, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol, or derivatives thereof.

Tablet cores may be provided with suitable, if need be enteric, coatings, using *inter alia* concentrated sugar solutions which may comprise gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, or coating solutions in suitable organic solvents or solvent mixtures, or, for the preparation of enteric coatings, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Dyes or pigments may be added to the tablets or tablet coatings, for example for identification purposes or to indicate different doses of active ingredient.

Orally administrable pharmaceutical compositions also include hard capsules consisting of gelatin, and also soft, sealed capsules consisting of gelatin and a plasticiser, such as glycerol or sorbitol. The hard capsules may contain the active ingredient in the form of granules, for example in admixture with fillers, such as corn starch, binders, and/or glidants, such as talc or magnesium stearate, and if need be stabilisers. In soft capsules, the active ingredient is preferably dissolved or suspended in suitable liquid excipients, such as fatty oils, paraffin oil or liquid polyethylene glycols or fatty acid esters of ethylene or propylene glycol, to which stabilisers and detergents, for example of the polyoxyethylene sorbitan fatty acid ester type, may also be added.

Other oral dosage forms are, for example, syrups prepared in customary manner which comprise the active ingredient, for example, in suspended form and in a concentration of about 5% to 20%, preferably about 10%, or in a similar concentration that provides a

suitable single dose, for example, when administered in measures of 5 or 10 ml. Also suitable are, for example, powdered or liquid concentrates for the preparation of shakes, for example in milk. Such concentrates may also be packaged in single dose quantities.

Suitable rectally administrable pharmaceutical compositions are, for example, suppositories that consist of a combination of the active ingredient and a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols.

The aqueous solutions suitable for parenteral administration are especially those of an active ingredient in water-soluble form, for example in the form of a water-soluble salt, or aqueous injection suspensions that contain viscosity-increasing substances, for example sodium carboxymethylcellulose, sorbitol and/or dextran, and, if need be, stabilisers. The active ingredient, if need be together with excipients, can also be in the form of a lyophilisate and can be made into a solution before parenteral administration by the addition of suitable solvents.

Solutions such as are used, for example, for parenteral administration can also be employed as infusion solutions.

Preferred preservatives are, for example, antioxidants, such as ascorbic acid, or microbicides, such as sorbic acid or benzoic acid.

Starting materials

The starting materials are known, commercially available, or capable of being prepared according to known processes, for example in a manner similar to the processes described in the Examples. This applies in particular to starting materials of formulae III, IV, V, VI, and VII.

For example, starting materials of formula III wherein X is hydroxy and hydrogen can be prepared according to, or in a manner similar to, one of the processes specified in US 4,935,415; EP 0 575 955; EP 0 238 011; or EP 0 383 919. Compounds of formula III wherein X is lower alkoxy and hydrogen can be prepared according to, or in a manner

similar to, EP 0 383 919. Compounds of formula III wherein X is oxo can be prepared according to, or in a manner similar to, EP 0 383 919. And compounds of formula III wherein at least one of the indices m and n is 1 or greater can be prepared according to, or in a manner similar to, one of the processes specified in US 7,677,429; WO 94/06799; US 5,461,146; EP 0 672 668; JP 05140168; or JO 3220-194.

Staurosporine of formula II itself is commercially available (Fluka, Buchs, Switzerland) and strains producing it have been filed for public access (for example the AM-2282 strain under FERM-P. No. 3725 (mentioned in J. Antibiotics XXX(4), 275 ff, 1977) and under NRRL 11,184 (*cf* US-Patent 4,107,297).

The cited references are incorporated insofar as is necessary.

Examples

The following Examples illustrate the invention without limiting the scope thereof.

The ratio of the solvents to one another in the mixtures of solvents or solvent systems used is indicated by volume (v/v), and temperatures are given in degrees celsius (°C). Temperatures are given in degrees celsius. Where no temperature is indicated, the reaction takes place in each case at room temperature.

The abbreviations used hereinafter have the following meanings:

bar	1 bar is equivalent to 10^5 pascal or 0.1 MPa (mega-pascal)
BOC	tert-butoxycarbonyl
°C	Degrees celsius
DMF	N,N'-dimethylformamide
Fp	melting point
MS (ESI)	Electrospray Ionisation Mass Spectroscopy (measurements are given as m/z)
h	hour(s)
Hexane	n-hexane
HPLC	high-pressure liquid chromatography

min	minute(s)
Pd/C 10 %	10% by weight of palladium on activated charcoal
Rh/Alox	rhodium on aluminium oxide
Rotavap	rotary evaporator
RT	room temperature
t_{Ret}	retention time on HPLC
THF	tetrahydrofuran
Tosyl	4-toluenesulfonyl
Dec.	under decomposition

For HPLC, a 250 x 4,6 mm reversed phase column with Nucleosil C18, 5 µm (Macherey & Nagel, Düren, Germany) is used. Gradient 1 is an acetonitrile-water gradient (in each case 0.1% trifluoroacetic acid in acetonitrile and water), in which the acetonitrile concentration is initially raised from 20% to 100% within 13 minutes and then eluted for 5 minutes with 100% acetonitrile. The elution takes place in an oven at 30°C. The detection takes place at 215 nm, and the flow rate is 1 ml/min.

Gradient 1: (= grad. 1) Acetonitrile-water gradient (in each case 0.1% trifluoroacetic acid in acetonitrile and water).
20→100% acetonitrile in 13 min + 5 min 100% acetonitrile

Gradient 4: (= grad. 4) Acetonitrile-water gradient (in each case 0.1% trifluoroacetic acid in acetonitrile and water).
2→100% acetonitrile in 10 min + 3 min 100% acetonitrile

Gradient 24: (= grad. 24) Acetonitrile-water gradient (in each case 0.1% trifluoroacetic acid in acetonitrile and water).
40% acetonitrile isocratic

Silica gel Si 60 is from Merck, Darmstadt, Germany.

The following are some educts which are obtainable from the suppliers indicated:

- Staurosporine, N-methylpiperazine, pyrrolidine, morpholine, piperazine, toluene-4-sulfochloride, trifluoroacetic anhydride, methyl bromoacetate, mono-methyl terephtalate, acrylonitrile, BOC-glycine, tert-butyl acrylate, BOC-L-alanine, 4-methoxyphenyl isocyanate, di-tert-butyl dicarbonate, 4-aminoethylmorpholine, phenyl chloroformate: Fluka, Buchs, Switzerland.
- N-Ethylpiperazine, ethyl 4-isocyanatobenzoate, sodium bis(trimethylsilyl)amide: Aldrich, Buchs, Switzerland.

Example 1: 1,2,3,4-Tetrahydrostaurosporine (1a) and 8,9,10,11-tetrahydrostaurosporine (1b)

20 g (42.89 mmol) staurosporine is hydrogenated in 1000 ml THF with the addition of 30 g Pd/C 10% (Engelhard, no. 4505, Italy, Rome) for 120 h at 65°C and 30 bar H_2. The suspension is filtered and washed with THF. The filtrate is concentrated by evaporation, and the residue in the flask is purified by chromatography using silica gel Si 60 (eluent: methylene chloride : methanol, 95:5). The crystals obtained are recrystallised from methanol. After filtration and drying, 1,2,3,4-tetrahydrostaurosporine (1a) is obtained as a white powder: Fp: 252-255°C. MS(ESI+): m/z= 471 $(M+H)^+$; HPLC:$t_{Ret.}$ (Grad. 1) = 8.83 min; HPLC:$t_{Ret.}$ (Grad. 24) = 10.08 min.

A further product in the form of 8,9,10,11-tetrahydrostaurosporine (1b) is also obtained as an amorphous beige powder: MS(ESI+): m/z= 471 $(M+H)^+$; HPLC:$t_{Ret.}$ (Grad.1) = 9.86 min; HPLC:$t_{Ret.}$ (Grad. 24) = 12.74 min.

Alternative synthesis 1: Alternatively, 1,2,3,4-tetrahydrostaurosporine (1a) may be prepared as follows: 3 g (6.43 mmol) staurosporine is hydrogenated in 150 ml isopropanol with the addition of 4.5 g Pd/C 10% for 38 h at 70°C and 60 bar H_2. After 22 h a further 4.5g Pd-C 10% is added. Analysis by HPLC shows the following composition:

1,2,3,4-Tetrahydrostaurosporine (1a) 58%
8,9,10,11-Tetrahydrostaurosporine (1b) : 2.6%
1,2,3,4,8,9,10,11-Octahydrostaurosporine : 2.2%

HPLC conditions:

Column: Nucleosil 100-3 C18 (Macherey & Nagel, Düren)

150 x 4,6 mm
Flow rate: 0.5 ml/min.
Detection: 215 nm
Oven temperature: 30°C
Gradient : Acetonitrile-water gradient (in each case 0.1% trifluoroacetic acid in acetonitrile and water): 25% acetonitrile isocratic

Alternative synthesis 2: 2 g (4.29 mmol) staurosporine is hydrogenated in 120 ml tetrahydrofuran with the addition of 2.0 g Rh/C 5% for 22 h at 80°C and 150 bar H_2. The catalyst is filtered off and washed with 200 ml tetrahydrofuran. The raw product is obtained as greenish crystals. Analysis by HPLC shows the following composition:

1,2,3,4-Tetrahydrostaurosporine: 80%
8,9,10,11-Tetrahydrostaurosporine: 2%
1,2,3,4,8,9,10,11-Octahydrostaurosporine: < 1%
Staurosporine: 17%

Alternative synthesis 3: 2 g (4.29 mmol) staurosporine is hydrogenated in 120 ml tetrahydrofuran with the addition of 0.25 ml acetic acid and 2.0 g Pd/C 10% for 33 h at 80°C and 150 bar H_2. The catalyst is filtered off and washed with 200 ml tetrahydrofuran. The raw product is obtained as greenish crystals. Analysis by HPLC shows the following composition:

1,2,3,4-Tetrahydrostaurosporine: 81%
8,9,10,11-Tetrahydrostaurosporine: 1%
1,2,3,4,8,9,10,11-Octahydrostaurosporine: < 1%
Staurosporine: 18%

HPLC conditions:
Column: Nucleosil 100-3 C18 (Macherey & Nagel, Düren, Germany)
Length 15 cm / diameter: 4.6 mm
Flow rate: 0.5 ml/min.
Detection: 215 nm
Oven temperature: 30°C
Gradient : Isocratic:

75% water (+ 0.1% TFA) / 25% acetonitrile (+ 0.1% TFA)

Example 2: N-[4-(4-Methylpiperazin-1-ylmethyl)benzoyl]-1,2,3,4-tetrahydrostaurosporine

42 mg (0.067 mmol) N-(4-chloromethylbenzoyl)-1,2,3,4-tetrahydrostaurosporine (Example 2.1), 8 mg (0.074 mmol) sodium carbonate, 0.075 ml (0.067 mmol) N-methylpiperazine, 1 ml THF, and 1 ml ethanol are stirred for 2½ h in an argon atmosphere at 85°C. After removal of the solvent, the residue is distributed twice between methylene chloride and water. The organic phases are combined, dried over Na_2SO_4, filtered, and concentrated by evaporation. The residue is recrystallised from methylene chloride / diethyl ether. After filtration and drying, the title compound is obtained as a beige powder: MS(ESI+): m/z= 687 $(M+H)^+$; HPLC: $t_{Ret.}$(Grad. 1)= 9.50 min.

The starting material is prepared as follows:

Step 2.1: N-(4-Chloromethylbenzoyl)-1,2,3,4-tetrahydrostaurosporine

A mixture of 400 mg (0.85 mmol) 1,2,3,4-tetrahydrostaurosporine (Example 1), 0.204 ml (1.19 mmol) N-ethyl diisopropylamine in 10 ml methylene chloride is mixed at RT with 193 mg (1.02 mmol) 4-chloromethyl benzoylchloride (Iharanikkei Chemical Industry Co., Ltd.). After 2 hours of stirring in an argon atmosphere at RT, the mixture is diluted with methylene chloride and extracted consecutively with 1N hydrochloric acid, saturated sodium bicarbonate solution, and water. The organic phase is dried over magnesium sulfate and filtered. After removal of the solvent, the residue is purified by chromatography using silica gel (eluent: methylene chloride : ethanol, 95 : 5). The title compound is obtained in the form of a beige powder. Fp: >350°C; MS(ESI+):m/z = 623 M^+; HPLC: $t_{Ret.}$(Grad. 1)=16.28min.

Example 3: N-(4-(Pyrrolidin-1-ylmethyl)benzoyl)-1,2,3,4-tetrahydrostaurosporine

The preparation is carried out in a manner analogous to that described in Example 2 starting from N-(4-chloromethylbenzoyl)-1,2,3,4-tetrahydrostaurosporine and pyrrolidine. The title compound is obtained in the form of a beige powder. Fp: 309-322°C; MS(ESI+): m/z= 658 $(M+H)^+$; HPLC: $t_{Ret.}$ (Grad. 1)=10.52 min.

Example 4: N-(4-(Morpholin-4-ylmethyl)benzoyl)-1,2,3,4-tetrahydrostaurosporine

The preparation is carried out in a manner analogous to that described in Example 2 starting from N-(4-chloromethylbenzoyl)-1,2,3,4-tetrahydrostaurosporine. The title

compound is obtained in the form of a beige powder. Fp: 219-222°C; MS(ESI+): m/z= 674 $(M+H)^+$; HPLC: $t_{Ret.}$ (Grad. 1)=10.35 min.

Example 5: N-(4-(Piperazin-1-ylmethyl)benzoyl)-1,2,3,4-tetrahydrostaurosporine

The preparation is carried out in a manner analogous to that described in Example 2 starting from N-(4-chloromethylbenzoyl)-1,2,3,4-tetrahydrostaurosporine (Example 2.1) and piperazine. The title compound is obtained as a beige powder. Fp: 305-312°C MS(ESI+): m/z= 673$(M+H)^+$; HPLC: $t_{Ret.}$ (Grad. 1)=9.28 min.

Example 6: N-Ethyl-1,2,3,4-tetrahydrostaurosporine

70 mg (0.149 mmol) 1,2,3,4-tetrahydrostaurosporine (Example 1), 43 mg (0.333 mmol) N-ethyl diisopropylamine and 52 mg (0.333 mmol) ethyl iodide are stirred in 1.5 ml DMF for 90 h at RT. After removal of the solvent, the residue is purified by chromatography using silica gel Si 60 (eluent: methylene chloride : methanol, 95:5). The crystals obtained are recrystallised from methylene chloride / diethyl. After filtration and drying, the title compound is obtained as a beige powder: MS(ESI+): m/z=500 $(M+H)^+$; HPLC:$t_{Ret.}$ (Grad. 1) = 9.96 min.

Example 7: N-Tosyl-1,2,3,4-tetrahydrostaurosporine

100 mg (0.212 mmol) 1,2,3,4-tetrahydrostaurosporine (Example 1) is dissolved in 2 ml chloroform and mixed with 49 mg (0.255 mmol) 4-toluenesulfonic acid chloride and 41 mg (0.319 mmol) N-ethyl diisopropylamine at RT. After 2 hours of stirring in an argon atmosphere at RT, the mixture is diluted with methylene chloride and extracted consecutively with saturated sodium bicarbonate solution and water. The organic phase is dried over magnesium sulfate and filtered. After removal of the solvent, the residue is purified by chromatography using silica gel (eluent: ethyl acetate : n-hexane, 3 : 2). The crystals obtained are recrystallised from methylene chloride / diethyl. After filtration and drying, the title compound is obtained as a white powder: Fp: 208-210°C; MS(ESI+): m/z=625 $(M+H)^+$; HPLC:$t_{Ret.}$ (Grad. 1) = 14.86 min.

Example 8: N-Triflouroacetyl-1,2,3,4-tetrahydrostaurosporine

The preparation is carried out in a manner analogous to that described in Example 7 starting from 1,2,3,4-tetrahydrostaurosporine (Example 1) and trifluoroacetic acid anhydride.

The title compound is obtained in the form of a white powder. Fp: 218-221°C; MS(ESI+): m/z=567 $(M+H)^+$; HPLC:$t_{Ret.}$ (Grad. 1) = 14.13 min.

Example 9: N-[4-(2-Imidazol-1-ylethoxy)benzoyl]-1,2,3,4-tetrahydrostaurosporine

100 mg (0.212 mmol) 1,2,3,4-tetrahydrostaurosporine (Example 1), 75 mg (0.254 mmol) 4-(2-imidazol-1-ylethoxy)benzoic acid nitrate, 49 mg (0.254 mmol) N-(3-dimethyl-aminopropyl)-N'-ethylcarbodiimide hydrochloride and 40 mg (0.254 mmol) 1-hydroxy-benzotriazole are stirred for 18 h in 2 ml DMF in an argon atmosphere at RT. After removal of the solvent, the residue is taken up in methylene chloride and consecutively extracted with sodium bicarbonate solution and water. The organic phases are combined, dried over magnesium sulfate, filtered, and concentrated by evaporation. After removal of the solvent, the residue is purified by chromatography using silica gel (eluent: methylene chloride : ethanol, 95 : 5). The crystals obtained are recrystallised from methylene chloride / diethyl. After filtration and drying, the title compound is obtained as a beige powder: Fp: 207-209°C; MS(ESI+): m/z= 685$(M+H)^+$; HPLC: $t_{Ret.}$ (Grad. 1)=10.51 min.

The starting material is prepared as follows:

9 a) 4-[2-(1H-Imidazol-1-yl)ethoxy]benzoic acid nitrate

1 g (3.62 mmol) 4-[2-(1H-imidazol-1-yl)ethoxy]benzonitrile (see J. Med. Chem. 28(10), 1427-32 (1985)), 0.434g (10.86 mmol) sodium hydroxide and 0.37 ml hydrogen peroxide 10% are stirred for 90 h in 10 ml ethanol under reflux. The resulting suspension is adjusted to pH 3 with 65% nitric acid, filtered, and washed to neutral with water. After filtration and drying, the title compound is obtained as white crystals: MS(ESI+):m/z= 233 (M+H)+; HPLC: t ret (Grad. 3)=8.25 min.

Example 10: N-Methoxycarbonylmethyl-1,2,3,4-tetrahydrostaurosporine

A mixture of 200 mg (0.424 mmol) 1,2,3,4-tetrahydrostaurosporine (Example 1), 78 mg (0.51 mmol) methyl bromoacetate, and 64 mg (0.49 mmol) N-ethyl diisopropylamine in 2 ml DMF is stirred for 26 h in an argon atmosphere at RT. With the addition of 2 ml water, the product is precipitated out and then recrystallised from ethyl acetate / hexane. After filtration and drying, the title compound is obtained as a beige powder: Fp: 214-218°C; MS(ESI+): m/z=543 $(M+H)^+$; HPLC:$t_{Ret.}$(Grad. 1) = 9.28 min.

Example 11: N-Carboxymethyl-1,2,3,4-tetrahydrostaurosporine

130 mg (0.24 mmol) N-methoxycarbonylmethyl-1,2,3,4-tetrahydrostaurosporine (Example 10) is stirred in 7 ml methanol and 0.21 ml (0.42 mmol) 2N sodium hydroxide solution for 5 h in an argon atmosphere under reflux. After removal of the solvent, the residue is taken up in methylene chloride and consecutively extracted with 1N hydrochloric acid and water. The organic phases are combined, dried over magnesium sulfate, filtered, and concentrated by evaporation. The residue is recrystallised from methanol / diethyl ether. After filtration and drying, the title compound is obtained as a beige powder: Fp: > 350°C (dec. from 310°C); MS(ESI+): m/z=529 $(M+H)^+$; HPLC:$t_{Ret.}$ (Grad. 1) = 8.49 min.

Example 12: N-Terephthaloyl methyl ester-1,2,3,4-tetrahydrostaurosporine (= N-(4-methoxycarbonylbenzoyl)-1,2,3,4-tetrahydrostaurosporine)

300 mg (0.63 mmol) 1,2,3,4-tetrahydrostaurosporine (Example 1), 126 mg (0.70 mmol) mono-methyl terephthalate (Fluka, Buchs, Switzerland) and 190 mg (1.16 mmol) diethyl cyanophosphonate are stirred in 5 ml DMF for 26 h in an argon atmosphere at RT. After removal of the solvent, the residue is taken up in methylene chloride and consecutively extracted with sodium bicarbonate solution and water. The organic phases are combined, dried over magnesium sulfate, filtered, and concentrated by evaporation. After removal of the solvent, the residue is purified by chromatography using silica gel (eluent: methylene chloride : ethanol, 95 : 5). The crystals obtained are recrystallised from methylene chloride / diethyl. After filtration and drying, the title compound is obtained as a beige powder: Fp: 228-232°C; MS(ESI+): m/z=633 $(M+H)^+$; HPLC:$t_{Ret.}$ (Grad. 1) = 13.80 min.

Example 13: N-Terephthaloyl-1,2,3,4-tetrahydrostaurosporine (= N-(4-carboxybenzoyl)-1,2,3,4-tetrahydrostaurosporine)

245 mg (0.39 mmol) N-Terephthaloyl methyl ester-1,2,3,4-tetrahydrostaurosporine (Example 12) is stirred in 6 ml methanol, 2 ml THF, 0.33 ml water, and 0.9 ml (0.9 mmol) 1N sodium hydroxide solution for 4½ h in an argon atmosphere under reflux. After removal of the solvent, the residue is taken up in methylene chloride and consecutively extracted with 1N hydrochloric acid and water. The organic phases are combined, dried over magnesium sulfate, filtered, and concentrated by evaporation. The residue is recrystallised from methanol / water. After filtration and drying, the title compound is obtained as a beige powder: Fp: 306-309°C; MS(ESI+): m/z=619 $(M+H)^+$; HPLC:$t_{Ret.}$ (Grad. 1) = 11.88 min.

Example 14: N-(4-Ethylpiperazinylcarbonylbenzoyl-1,2,3,4-tetrahydrostaurosporine

105 mg (0.17 mmol) N-terephthaloyl-1,2,3,4-tetrahydrostaurosporine (Example 13), 39 mg (0.34 mmol) N-ethylpiperazine and 55 mg (0.34 mmol) diethyl cyanophosphonate are stirred in 2 ml DMF for 22 h in an argon atmosphere at RT. After removal of the solvent, the residue is taken up in methylene chloride and consecutively extracted with sodium bicarbonate solution and water. The organic phases are combined, dried over magnesium sulfate, filtered, and concentrated by evaporation. The crystals obtained are recrystallised from methylene chloride / diethyl. After filtration and drying, the title compound is obtained as a beige powder: Fp: 224-227°C; MS(ESI+): m/z=715 $(M+H)^+$; HPLC:$t_{Ret.}$ (Grad. 1) = 9.39 min.

Example 15: N-(2-Cyanoethyl)-1,2,3,4-tetrahydrostaurosporine

A suspension of 100 mg (0.21 mmol) 1,2,3,4-tetrahydrostaurosporine (Example 1) in 2.5 ml (40 mmol) acrylonitrile is stirred in a sealed tube for 44 h at 140°C. After cooling, the reaction mixture is concentrated by evaporation and purified by chromatography using silica gel (eluent: methylene chloride : ethanol, 95 : 5) The crystals obtained are recrystallised from methylene chloride / diethyl. After filtration and drying, the title compound is obtained as a beige powder: Fp: 229-231°C; MS(ESI+): m/z=524 $(M+H)^+$; HPLC:$t_{Ret.}$ (Grad. 1) = 9.17 min.

Example 16: N-Benzoyl-1,2,3,4-tetrahydrostaurosporine

The preparation is carried out in a manner analogous to that described in Example 7 starting from 1,2,3,4-tetrahydrostaurosporine (Example 1) and benzoyl chloride. The title compound is obtained in the form of a beige powder. Fp: 228-232°C; MS(ESI+): m/z=575 $(M+H)^+$; HPLC:$t_{Ret.}$ (Grad. 1) = 13.90 min.

Example 17: N,N-Dimethyl -1,2,3,4-tetrahydrostaurosporinium iodide

A mixture of 200 mg (0.425 mmol) 1,2,3,4-tetrahydrostaurosporine (Example 1), 135 mg (0.950 mmol) methyl iodide, and 123 mg (0.950 mmol) N-ethyl diisopropylamine is stirred for 48 h in an argon atmosphere at RT. The precipitate obtained is filtered off by suction and washed with methylene chloride. After drying, the title compound is obtained as a white

powder: Fp: dec. from 270°C; MS(ESI+): m/z=499 $(M+H)^+$; HPLC:$t_{Ret.}$ (Grad. 1) = 9.17 min.

Example 18: N-BOC-glycyl-1,2,3,4-tetrahydrostaurosporine

A mixture of 200 mg (0.425 mmol) 1,2,3,4-tetrahydrostaurosporine (Example 1), 82 mg (0.46 mmol) BOC-glycine, and 114 mg (0.55 mmol) N,N'-dicyclohexylcarbodiimide in 10 ml chloroform is stirred for 17 h in an argon atmosphere at RT. After dilution with methylene chloride, extraction is performed with sodium bicarbonate solution and water consecutively. The organic phases are combined, dried over magnesium sulfate, filtered, and concentrated by evaporation. After removal of the solvent, the residue is purified by chromatography using silica gel (eluent: toluene : acetone, 4 : 1). The crystals obtained are recrystallised from methylene chloride / diethyl. After filtration and drying, the title compound is obtained as a beige powder: Fp: 208-210°C; MS(ESI+): m/z= 628$(M+H)^+$; HPLC: $t_{Ret.}$ (Grad. 1)=13.19 min.

Example 19: N-Glycyl-1,2,3,4-tetrahydrostaurosporine hydrochloride

120 mg (0.19 mmol) N-BOC-glycyl-1,2,3,4-tetrahydrostaurosporine (Example 18) is dissolved in 1 ml 1,4-dioxane, mixed with 1 ml 4N HCl in dioxane, and stirred for 4½ h in an argon atmosphere at RT. The precipitate obtained is filtered off and washed with diethyl ether. After drying, the title compound is obtained as a beige powder: Fp: dec. from 290°C; MS(ESI+): m/z= 528$(M+H)^+$; HPLC: $t_{Ret.}$ (Grad. 1)=8.72 min.

Example 20: N-(3-(tert-Butoxycarbonyl)propyl)-1,2,3,4-tetrahydrostaurosporine

A suspension of 300 mg (0.64 mmol) 1,2,3,4-tetrahydrostaurosporine (Example 1) in 4 ml (27.5 mmol) tert-butyl acrylate is stirred in a sealed tube for 44 h at 140°C. After cooling, the reaction mixture is concentrated by evaporation and purified by chromatography using silica gel (eluent: toluene : acetone, 4 : 1) The crystals obtained are recrystallised from methylene chloride / diethyl ether / n-hexane. After filtration and drying, the title compound is obtained as a beige powder: Fp: 144-147°C; MS(ESI+): m/z=599 $(M+H)^+$;HPLC:$t_{Ret.}$ (Grad. 1) = 11.11 min.

Example 21: N-(3-Carboxypropyl)-1,2,3,4-tetrahydrostaurosporine trifluoroacetate

55 mg (0.092 mmol) N-(3-(tert-butoxycarbonyl)propyl)-1,2,3,4-tetrahydrostaurosporine (Example 20) is dissolved in 1 ml methylene chloride, mixed with 0.25 ml trifluoroacetic acid, and stirred for 8½ h in an argon atmosphere at RT. After removal of the solvent, the residue is recrystallised from methylene chloride / diethyl ether. After filtration and drying, the title compound is obtained as a beige powder: Fp: dec. from 280°C; MS(ESI+): m/z= 543$(M+H)^+$; HPLC: $t_{Ret.}$ (Grad. 1)=8.80 min.

Example 22: N-(4-(Imidazol-1-yl)benzoyl)-1,2,3,4-tetrahydrostaurosporine

100 mg (0.212 mmol) 1,2,3,4-tetrahydrostaurosporine (Example 1), 57 mg (0.254 mmol) 4-(imidazol-1-yl)benzoic acid potassium salt (see WO 95/04729), 49 mg (0.254 mmol) N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride and 40 mg (0.254 mmol) 1-hydroxybenzotriazole are stirred for 24 h in 2 ml DMF in an argon atmosphere at RT. After removal of the solvent, the residue is taken up in methylene chloride and consecutively extracted with sodium bicarbonate solution and water. The organic phases are combined, dried over magnesium sulfate, filtered, and concentrated by evaporation. The residue is purified by chromatography using silica gel (eluent: methylene chloride : ethanol, 95:5). The crystals obtained are recrystallised from methylene chloride / diethyl. After filtration and drying, the title compound is obtained as a beige powder: Fp: 257-261°C; MS(ESI+): m/z= 641$(M+H)^+$; HPLC: $t_{Ret.}$ (Grad. 1)=9.99 min.

Example 23: N-[(Tetrahydro-2H-pyran-4-yloxy)acetyl]-1,2,3,4-tetrahydrostaurosporine

235 mg (0.50 mmol) 1,2,3,4-tetrahydrostaurosporine (Example 1), 100 mg (0.625 mmol) tetrahydro-2H-pyran-4-yloxyacetic acid (see EP 0 624 590), 155 mg (0.81 mmol) N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride and 122 mg (0.81 mmol) 1-hydroxybenzotriazole are stirred for 18 h in 5 ml DMF in an argon atmosphere at RT. After removal of the solvent, the residue is purified by chromatography using silica gel (eluent: methylene chloride : ethanol, 98:2). The crystals obtained are recrystallised from methylene chloride / diethyl. After filtration and drying, the title compound is obtained as a beige powder: Fp: 197-199°C; MS(ESI+): m/z= 613 $(M+H)^+$; HPLC: $t_{Ret.}$ (Grad. 1)=12.27 min.

Example 24: N-BOC-L-alanyl-1,2,3,4-tetrahydrostaurosporine

A mixture of 235 mg (0.50 mmol) 1,2,3,4-tetrahydrostaurosporine (Example 1), 123 mg (0.65 mmol) BOC-L-alanine, 117 mg (0.78 mmol) 1-hydroxybenzotriazole, and 161 mg

(0.78 mmol) N,N'-dicyclohexylcarbodiimide in 5 ml DMF is stirred for 17 h in an argon atmosphere at RT. After removal of the solvent, the residue is purified by chromatography using silica gel (eluent: methylene chloride : ethanol, 98:2). The crystals obtained are recrystallised from methylene chloride / diethyl. After filtration and drying, the title compound is obtained as a beige powder: Fp: 305-312°C; MS(ESI+): m/z= 642$(M+H)^+$; HPLC: $t_{Ret.}$ (Grad. 1)=14.07 min.

Example 25: N-L-Alanyl-1,2,3,4-tetrahydrostaurosporine hydrochloride

70 mg (0.109 mmol) N-BOC-alanyl-1,2,3,4-tetrahydrostaurosporine (Example 24) is stirred for 2 h in 3 ml 4N HCl in dioxane in an argon atmosphere at RT. The precipitate obtained is filtered off and washed with diethyl ether. After drying, the title compound is obtained as a beige powder: Fp: dec. from 290°C; MS(ESI+): m/z= 542$(M+H)^+$; HPLC: $t_{Ret.}$ (Grad. 1)=9.09 min.

Example 26: N-Methyl-1,2,3,4-tetrahydro-6-methyl-staurosporine

A mixture of 200 mg (0.425 mmol) 1,2,3,4-tetrahydrostaurosporine (Example 1), 981 mg (12.09 mmol) formaldehyde 37%, 1575 mg (26.22 mmol) glacial acetic acid, and 600 mg (8.10 mmol) sodium cyanoborohydride in 10 ml acetonitrile is stirred for 72 h in an argon atmosphere at RT. After removal of the solvent, the residue is purified by chromatography using silica gel (eluent: methylene chloride : ethanol, 98:2). The crystals obtained are recrystallised from methylene chloride / diethyl. After filtration and drying, the title compound is obtained as a beige powder: Fp: 273-275°C; MS(ESI+): m/z= 499$(M+H)^+$; HPLC: $t_{Ret.}$ (Grad. 1)=9.80 min.

Example 27: N-(4-Carboxyphenylaminocarbonyl)-1,2,3,4-tetrahydrostaurosporine

100 mg (0.15 mmol) N-(4-ethoxycarbonylphenylaminocarbonyl)-1,2,3,4-tetrahydrostaurosporine (Example 28), 200 mg (8.32 mmol) lithium hydroxide, and 10 ml methanol are stirred for 4 h in an argon atmosphere at 85°C. After removal of the solvent, the residue is distributed twice between methylene chloride and 10% citric acid solution. The organic phases are combined, dried over Na_2SO_4, filtered, and concentrated by evaporation. The residue is recrystallised from methylene chloride / diethyl ether. After filtration and drying, the title compound is obtained as a beige powder: MS(ESI+): m/z= 634 $(M+H)^+$; HPLC: $t_{Ret.}$(Grad. 4)= 7.67 min.

Example 28: N-(4-Ethoxycarbonylphenylaminocarbonyl)-1,2,3,4-tetrahydrostaurosporine

A mixture of 200 mg (0.43 mmol) 1,2,3,4-tetrahydrostaurosporine (Example 1), and 98.6 mg (0.51 mmol) ethyl-4-isocyanatobenzoate is stirred for 5 h in 4 ml chloroform in a nitrogen atmosphere at 50°C. The mixture is then concentrated in the Rotavap and the residue purified by chromatography using silica gel (eluent: methylene chloride : ethanol, 95:5). The title compound is obtained as a beige powder. Fp: >300°C; MS(ESI+):m/z = 662; HPLC: $t_{Ret.}$(Grad. 4)=9.19min.

Example 29: N-(N-Phenylaminocarbonyl)-1,2,3,4-tetrahydrostaurosporine

116 mg (0.25 mmol) 1,2,3,4-tetrahydrostaurosporine and 0.033 ml phenyl isocyanate are stirred for 15 min in 3 ml chloroform at 20°C in an argon atmosphere. After removal of the solvent, the residue is distributed twice between methylene chloride and water. The organic phases are combined, dried over magnesium sulfate, filtered, and concentrated by evaporation. The residue is recrystallised from methylene chloride / ethanol. After filtration and drying, the said product is obtained as a beige powder: Fp: >300°C; MS(ESI+): m/z= 590 $(M+H)^+$; HPLC: $t_{Ret.}$ (Grad. 4)=8.7 min.

Example 30: N-(N-[2-(1-Morpholino)ethyl]-aminocarbonyl)-1,2,3,4-tetrahydrostaurosporine

200 mg (0.43 mmol) 1,2,3,4-tetrahydrostaurosporine and 750 mg (3 mmol) (2-morpholin-4-ylethyl)carbamic acid phenyl ester are stirred for 2 h at 100°C in an argon atmosphere. After cooling to RT, the residue is distributed twice between ethyl acetate and 1N NaOH. The organic phases are combined, dried over magnesium sulfate, filtered, and concentrated by evaporation. The residue is purified on silica gel (eluent: ethyl acetate : ethanol, 9 : 1). After evaporation, the title compound is obtained as an amorphous beige powder: MS(ESI+): m/z= 627 $(M+H)^+$; HPLC: $t_{Ret.}$ (Grad. 4)=6.2 min.

The starting material is prepared as follows:

30 a) (2-Morpholin-4-ylethyl)carbamic acid phenyl ester

1.3 ml (10 mmol) aminoethylmorpholine is cooled in 50 ml THF and 1.4 ml (10 mmol) triethylamine to 0°C. At 0–5°C, 1.0 ml (10 mmol) phenyl chloroformate is added dropwise and the mixture then stirred for another 30 min at RT. The reaction mixture is distributed twice between ethyl acetate and 1N sodium hydroxide in water and once with phosphate

buffer pH 7. The organic phases are combined, dried over magnesium sulfate, filtered, and concentrated by evaporation. The title compound, which is obtained as a brown product, is immediately reused.

Example 31: N-(N-[4-Methoxyphenyl]aminocarbonyl)-1,2,3,4-tetrahydrostaurosporine

In the manner described in Example 29, the title compound is prepared starting from 4-methoxyphenyl isocyanate. Fp: >300°C; MS(ESI+): m/z= 621$(M+H)^+$; HPLC: $t_{Ret.}$ (Grad. 4)=8.46 min.

Example 32: 1,2,3,4-Tetrahydro-6-methyl-staurosporine

200 mg (0.34 mmol) N-BOC-1,2,3,4-tetrahydro-6-methylstaurosporine (Example 34) and 1.5 ml 4N chlorohydrocarbon in dioxane were stirred for 4h at RT. After removal of the solvent, the residue is distributed twice between ethyl acetate and 10% sodium bicarbonate. The organic phases are combined, dried over magnesium sulfate, filtered, and concentrated by evaporation. The residue is purified by chromatography using silica gel (eluent: ethyl acetate : EtOH, 9 : 1). After evaporation, the title compound is obtained as an amorphous beige powder: MS(ESI+): m/z=485 $(M+H)^+$; HPLC:$t_{Ret.}$ (Grad. 4) = 6.49 min.

Example 33: N-BOC-1,2,3,4-tetrahydrostaurosporine

500 mg (1.06 mmol) 1,2,3,4-tetrahydrostaurosporine, 279 mg (1.28 mmol) BOC-anhydride (di-tert-butyl dicarbonate) and 10 ml THF are stirred for 17 h at 20°C in an argon atmosphere. After removal of the solvent, the residue is recrystallised from THF / diethyl ether. After filtration and drying, the title compound is obtained as a beige powder: Fp: amorphous; MS(ESI+): m/z= 571$(M+H)^+$; HPLC: $t_{Ret.}$ (Grad. 4)=9.8 min.

Example 34: N-BOC-1,2,3,4-tetrahydro-6-methylstaurosporine

400 mg (0.7 mmol) N-BOC-1,2,3,4-tetrahydrostaurosporine (Example 33), 0.8 ml sodium bis(trimethylsilyl)amide and 2 ml DMF are stirred for 90 min at 20°C in an argon atmosphere. 0.052 ml methyl iodide dissolved in 1 ml DMF is added, and the mixture stirred for a further 2 h at 20°C. The reaction mixture is poured over ice and distributed twice between ethyl acetate and 1N hydrochloric acid. The organic phases are combined, dried over magnesium sulfate, filtered, and concentrated by evaporation. The residue is purified by chromotography using silica gel (eluent: ethyl acetate : hexane, 1:1). After evaporation,

the title compound is obtained as an amorphous beige powder: MS(ESI+):m/z=585(M+H); HPLC:$t_{Ret.}$ (Grad. 4) = 10.44 min.

Example 35: N-BOC-1,2,3,4-tetrahydro-6-methyl-7-oxo-staurosporine

As by-product, the title compound is obtained as a beige powder from Example 34. MS(ESI+):m/z=599(M+H): HPLC:$t_{Ret.}$ (Grad. 4) = 12.02 min.

Example 36: 1,2,3,4,8,9,10,11-Octahydrostaurosporine:

4 g (8.57 mmol) staurosporine is hydrogenated in 400 ml tert-butanol with the addition of 4 g Rh/Alox 10% (Engelhard, 4824, England) for 20 h at 130°C and 100 bar H_2. The suspension is filtered and washed with tert-butanol. The filtrate is concentrated by evaporation, and the residue in the flask is purified by chromatography using silica gel Si 60 (eluent: methylene chloride : methanol, 95:5). The crystals obtained are recrystallised from methanol. After filtration and drying, 1,2,3,4,8,9,10,11-octahydrostaurosporine is obtained as an amorphous beige powder: MS(ESI+): m/z= 475 $(M+H)^+$; HPLC:$t_{Ret.}$ (Grad.1) = 9.76 min; HPLC:$t_{Ret.}$ (Grad. 24) = 11.74 min.

Example 37: Tablets containing 20 mg of active substance, for example one of the compounds of formula I described in the aforesaid Examples, especially the title compound from Example 1a, are manufactured in the following composition in the usual manner:

Composition

Active ingredient	20 mg
Wheat starch	60 mg
Lactose	50 mg
Colloidal silica	5 mg
Talc	9 mg
Magnesium stearate	1 mg
	(145 mg)

Preparation: The active substance is mixed with part of the wheat starch, with lactose and colloidal silica, and the mixture passed through a sieve. A paste is formed with another part

of the wheat starch and 5 times its volume of water on a water bath, and the powder mixture is kneaded with this paste until a weakly pliant mass is obtained.

The pliant mass is pressed through a sieve with a mesh size of about 3 mm, dried, and the dry granulate thus obtained is passed through the sieve again. The remaining wheat starch, talc, and magnesium stearate are mixed in, and the mixture is compressed to form scored tablets with a weight of 145 mg.

Example 38: Determination of water solubility:

According to the process described in the general description above, the following water solubilities are found for the following Examples:

Example (as methanesulfonate salt)	Solubility (% by weight)
1a	> 100

Example 39: Inhibition of PKC-α

According to the process described hereinbefore for the PKC isozyme PKC-α, the following inhibitory constants are obtained (indicated only where a concrete value was determined):

Compound from Example	IC_{50} (μmol)
1a	0.050
1b	0.5
3	0.73
5	0.68
6	0.06
7	about 1
8	0.26
9	0.44
10	0.43
11	0.07
12	0.61
13	0.04
14	0.33

15	0.23
16	0.22
17	0.026
18	0.28
19	0.08
20	1
21	0.07
22	0.14
23	0.1
24	0.9
25	0.083
26	0.050
27	0.034
28	about 1
29	0.15
30	0.24
31	0.17
32	0.62
33	about 1
36	0.58

Example 40: Inhibition of the growth of T24 bladder carcinoma cells

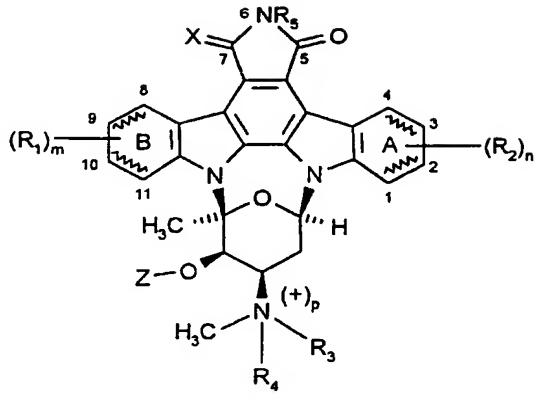
According to the process described hereinbefore, the following concentrations are determined for the inhibition of the growth of T24 cells (indicated only where a concrete value was determined):

Compound from Example	IC_{50} (µmol)
1a	0.004
1b	<0.020
2	0.13
3	0.39
4	0.43
5	0.45

6	about 0.01
8	0.021
9	0.20
10	0.22
11	0.009
12	0.76
13	1.4
14	0.63
15	0.43
16	0.49
17	0.34
18	0.38
19	0.11
20	0.23
21	0.38
22	0.049
23	0.19
24	0.50
25	0.057
26	3.4
27	0.17
28	0.046
29	0.036
30	0.18
31	0.018
32	0.042
33	2.7
36	0.038

What is claimed is

1. A compound of formula I



(I)

wherein R_1 and R_2 are, independently of one another, unsubstituted or substituted alkyl, halogen, hydroxy, etherified or esterified hydroxy, amino, mono- or disubstituted amino, cyano, nitro, mercapto, substituted mercapto, carboxy, esterified carboxy, carbamoyl, N-mono- or N,N-di-substituted carbamoyl, sulfo, substituted sulfonyl, aminosulfonyl or N-mono- or N,N-di-substituted aminosulfonyl;

n and m are, independently of one another, a number from and including 0 to and including 4;

R_3 and R_4 are, independently of one another, hydrogen, an aliphatic, carbocyclic, or carbocyclic-aliphatic radical with up to 29 carbon atoms in each case, a heterocyclic or heterocyclic-aliphatic radical with up to 20 carbon atoms in each case, and in each case up to 9 heteroatoms, wherein R_4 may also be absent;

or R_3 is acyl with up to 30 carbon atoms and R_4 is absent;

p is 0 if R_4 is absent, or is 1 if R_3 and R_4 are both present and in each case are one of the aforementioned radicals;

R_5 is hydrogen, an aliphatic, carbocyclic, or carbocyclic-aliphatic radical with up to 29 carbon atoms in each case, or a heterocyclic or heterocyclic-aliphatic radical with up to 20 carbon atoms in each case, and in each case up to 9 heteroatoms, or acyl with up to 30 carbon atoms;

X stands for 2 hydrogen atoms; for 1 hydrogen atom and hydroxy; for O; or for hydrogen and lower alkoxy;

Z stands for hydrogen or lower alkyl;

and either the two bonds characterised by wavy lines are absent in ring A and replaced by 4 hydrogen atoms, and the two wavy lines in ring B each, together with the respective parallel bond, signify a double bond;

or the two bonds characterised by wavy lines are absent in ring B and replaced by a total of 4 hydrogen atoms, and the two wavy lines in ring A each, together with the respective parallel bond, signify a double bond;

or both in ring A and in ring B all of the 4 wavy bonds are absent and are replaced by a total of 8 hydrogen atoms;

or a salt thereof, if at least one salt-forming group is present.

2. A compound of formula I according to claim 1, wherein
R_1 and R_2 independently of each other are lower alkyl, lower alkyl substituted by halogen, C_6-C_{14}aryl, hydroxy, lower alkoxy, phenyl-lower alkoxy, phenyloxy, lower alkanoyloxy, benzoyloxy, amino, lower alkylamino, lower alkanoylamino, phenyl-lower alkylamino, N,N-di-lower alkylamino, N,N-di-(phenyl-lower alkyl)amino, cyano, mercapto, lower alkylthio, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkyl-carbamoyl, sulfo, lower alkanesulfonyl, lower alkoxysulfonyl, aminosulfonyl, N-lower alkylaminosulfonyl or N,N-di-lower alkylaminosulfonyl; halogen; lower alkoxy; C_6-C_{14}aryloxy; C_6-C_{14}aryl-lower alkoxy; lower alkanoyloxy; C_6-C_{14}arylcarbonyloxy; amino monosubstituted or disubstituted by lower alkyl, C_6-C_{14}aryl, C_6-C_{14}aryl-lower alkyl, lower alkanoyl or C_6-C_{12}-

arylcarbonyl; cyano; nitro; mercapto; lower alkylthio; C_6-C_{14}arylthio; C_6-C_{14}aryl-lower alkylthio; lower alkanoylthio; C_6-C_{14}aryl-lower alkanoylthio; carboxy; lower alkoxycarbonyl, C_6-C_{14}aryl-lower alkoxycarbonyl; C_6-C_{14}aryloxycarbonyl; carbamoyl; carbamoyl N-mono- or N,N-disubstituted by lower alkyl, C_6-C_{14}aryl or C_6-C_{14}aryl-lower alkyl; sulfo; C_6-C_{14}aryl-sulfonyl; C_6-C_{14}aryl-lower alkanesulfonyl; lower alkanesulfonyl; or aminosulfonyl N-mono- or N,N-disubstituted by lower alkyl, C_6-C_{14}aryl or C_6-C_{14}aryl-lower alkyl, wherein C_6-C_{14}aryl is an aryl radical with 6 to 12 carbon atoms in the ring system, which may be unsubstituted or substituted by halogen, phenyl or naphthyl, hydroxy, lower alkoxy, phenyl-lower alkoxy, phenyloxy, lower alkanoyloxy, benzoyloxy, amino, lower alkylamino, lower alkanoylamino, phenyl-lower alkylamino, N,N-di-lower alkylamino, N,N-di-(phenyl-lower alkyl)amino, cyano, mercapto, lower alkylthio, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkyl-carbamoyl, N,N-di-lower alkylcarbamoyl, sulfo, lower alkanesulfonyl, lower alkoxysulfonyl, aminosulfonyl, N-lower alkylaminosulfonyl or N,N-di-lower alkylaminosulfonyl;

n and m independently of each other are 0 or 1;

R_3 and R_4 independently of each other are

hydrogen,

lower alkyl, lower alkenyl, or lower alkadienyl, which in each case are unsubstituted or monosubstituted or polysubstituted by a substituent independently selected from lower alkyl; hydroxy; lower alkoxy, which may be unsubstituted or mono-, di-, or trisubstituted by (i) heterocyclyl with 4 to 12 ring atoms, which may be unsaturated, wholly saturated, or partly saturated, is monocyclic or bicyclic and may contain up to three heteroatoms selected from nitrogen, oxygen and sulfur, (ii) by halogen, (iii) by hydroxy or (iv) by lower alkoxy; phenoxy; phenyl-lower alkoxy; heterocyclyloxy, wherein heterocyclyl is pyrrolyl, pyridyl, thienyl, furyl, indolyl, quinolyl, isoquinolyl, benzofuranyl, chromenyl, benzothienyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl, thiazolyl, benzimidazolyl, benzoxazolyl, quinazolyl, 2-tetrahydrofuryl, 4-tetrahydrofuryl, 2- or 4-tetrahydropyranyl, 1-, 2- or 3-pyrrolidyl, 1-, 2-, 3-, or 4-piperidyl, 1-, 2-or 3-morpholinyl, 2- or 3-thiomorpholinyl, 2-piperazinyl or N,N'-bis-lower alkyl-2-piperazinyl; lower alkanoyloxy; carboxy; lower alkoxycarbonyl; phenyl-lower alkoxycarbonyl; mercapto; lower alkylthio; phenylthio; halogen; halogen-lower alkyl; oxo

(except in the 1-position, because otherwise acyl); azido; nitro; cyano; amino; mono-lower alkylamino; di-lower alkylamino; pyrrolidino; imidazol-1-yl; piperidino; piperazino; 4-lower alkylpiperazino; morpholino; thiomorpholino; diphenylamino or dibenzylamino unsubstituted or substituted in the phenyl part by lower alkyl, lower alkoxy, halogen and/or nitro; lower alkoxycarbonylamino; phenyl-lower alkoxycarbonylamino unsubstituted or substituted in the phenyl part by lower alkyl or lower alkoxy; fluorenylmethoxycarbonylamino; amino-lower alkyl; monosubstituted or disubstituted amino-lower alkyl, wherein the amino substituent is selected from lower alkyl, hydroxy-lower alkyl, C_3-C_8cycloalkyl, amino-lower alkyl, N-mono- or N,N-di(-lower alkyl)amino-lower alkyl, amino, N-mono- or N,N-di-lower alkylamino and N-mono- or N,N-di-(hydroxy-lower alkyl)amino; pyrrolidino-lower alkyl; piperidino-lower alkyl; piperazino-lower alkyl; 4-lower alkylpiperazino-lower alkyl; imidazol-1-yl-lower alkyl; morpholino-lower alkyl; thiomorpholino-lower alkyl; S-oxo-thiomorpholino-lower alkyl; S,S-dioxothiomorpholino-lower alkyl; lower alkylendioxy; sulfamoyl; sulfo; carbamoyl; ureido; guanidino; cyano; aminocarbonyl, which is substituted by one or two radicals on the nitrogen, wherein the amino substituents are selected independently of one another from the group comprising lower alkyl, hydroxy-lower alkyl, C_3-C_8cycloalkyl, amino-lower alkyl, N-mono- or N,N-di(-lower alkyl)amino-lower alkyl, amino, N-mono- or N,N-di-lower alkylamino and N-mono- or N,N-di-(hydroxy-lower alkyl)amino; pyrrolidinocarbonyl; piperidinocarbonyl; piperazinocarbonyl; 4-lower alkylpiperazinocarbonyl; imidazolinocarbonyl; morpholino-carbonyl; thiomorpholinocarbonyl; S-oxo-thiomorpholinocarbonyl; and S,S-dioxothio-morpholino;

phenyl, naphthyl, phenyl-lower alkyl or phenyl-lower alkenyl with a terminal phenyl radical, which is unsubstituted or monosubstituted or disubstituted by the radicals named above as substituents of lower alkyl, lower alkenyl or lower alkadienyl;

or heterocyclyl-lower alkyl, wherein heterocyclyl is pyrrolyl, pyridyl, thienyl, furyl, furyl, indolyl, quinolyl, isoquinolyl, benzofuranyl, chromenyl, benzothienyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl, thiazolyl, benzimidazolyl, benzoxazolyl, quinazolyl, 2-tetrahydrofuryl, 4-tetrahydrofuryl, 2- or 4-tetrahydropyranyl, 1-, 2- or 3-pyrrolidyl, 1-, 2-, 3-, or 4-piperidyl, 1-, 2- or 3-morpholinyl, 2- or 3-thiomorpholinyl, 2-piperazinyl or N,N'-bis-lower alkyl-2-piperazinyl, which in each case are unsubstituted or monosubstituted or disubstituted by the radicals named hereinabove as substituents of lower alkyl, lower alkenyl or lower alkadienyl;

whereby R_4 may also be absent:

or
R_4 is absent, and

R_3 is acyl of the subformulae Y-C(=W)-, wherein W is oxygen and Y is hydrogen, R°, R°-O-, R°HN-, or R°R°N- (wherein the radicals R° may be the same or different),

or
is acyl of the subformula $R°-SO_2-$,

wherein R° in the said radicals has the following meanings: lower alkyl; amino-lower alkyl, wherein the amino group is present in unprotected form or is protected by a conventional amino protecting group; carboxy-lower alkyl; lower alkoxycarbonyl-lower alkyl; cyano-lower alkyl; tetrahydropyranyloxy-lower alkyl; morpholino-lower alkyl; phenyl; lower alkylphenyl; lower alkoxyphenyl; imidazolyl-lower alkoxyphenyl; carboxyphenyl; lower alkoxycarbonyl-phenyl; halogen-lower alkylphenyl; pyrrolidinophenyl; imidazol-1-ylphenyl; piperazinophenyl; (4-lower alkylpiperazino)-phenyl; morpholinophenyl; pyrrolidino-lower alkylphenyl; imidazol-1-yl-lower alkylphenyl; piperazino-lower alkylphenyl; (4-lower alkylpiperazinomethyl)phenyl; morpholinomethylphenyl; piperazinocarbonylphenyl; or (4-lower alkylpiperazino)phenyl;

p is 0 if R_4 is absent, or is 1 if R_3 and R_4 are both present and in each case are one of the aforementioned radicals;

R_5 is hydrogen or lower alkyl;

X stands for 2 hydrogen atoms; for O; for 1 hydrogen atom and hydroxy; or for 1 hydrogen atom and lower alkoxy;

Z stands for hydrogen or lower alkyl;

and either the two bonds characterised by wavy lines are absent in ring A and replaced by 4 hydrogen atoms, and the two wavy lines in ring B each, together with the respective parallel bond, signify a double bond;

or the two bonds characterised by wavy lines are absent in ring B and replaced by a total of 4 hydrogen atoms, and the two wavy lines in ring A each, together with the respective parallel bond, signify a double bond;

or both in ring A and in ring B all of the 4 wavy bonds are absent and are replaced by a total of 8 hydrogen atoms;

or a salt thereof, if at least one salt-forming group is present.

3. A compound of formula I according to claim 1, wherein
m and n are each 0;

R_3 and R_4 are independently of each other

hydrogen,

lower alkyl unsubstituted or mono- or disubstituted by radicals selected independently of one another from carboxy; lower alkoxycarbonyl; and cyano; whereby R_4 may also be absent;

or

R_4 is absent, and

R_3 is acyl of the subformula R°-CO, wherein R° is lower alkyl; amino-lower alkyl, wherein the amino group is present in unprotected form or is protected by lower alkoxycarbonyl; tetrahydropyranyloxy-lower alkyl; phenyl; imidazolyl-lower alkoxyphenyl; carboxyphenyl; lower alkoxycarbonylphenyl; halogen-lower alkylphenyl; imidazol-1-ylphenyl; pyrrolidino-

lower alkylphenyl; piperazino-lower alkylphenyl; (4-lower alkylpiperazinomethyl)phenyl; morpholino-lower alkylphenyl; piperazinocarbonylphenyl; or (4-lower alkylpiperazino)phenyl;

or is acyl of the subformula R°-O-CO-, wherein R° is lower alkyl;

or is acyl of the subformula R°HN-C(=W)-, wherein W is oxygen and R° has the following meanings: morpholino-lower alkyl, phenyl, lower alkoxyphenyl, carboxyphenyl, or lower alkoxycarbonylphenyl;

or R_3 is lower alkylphenylsulfonyl, typically 4-toluenesulfonyl;

p is 0 if R_4 is absent, or is 1 if R_3 and R_4 are both present and in each case are one of the aforementioned radicals;

R_5 is hydrogen or lower alkyl;

X stands for 2 hydrogen atoms or for O;

Z is methyl;

and either the two bonds characterised by wavy lines are absent in ring A and replaced by 4 hydrogen atoms, and the two wavy lines in ring B each, together with the respective parallel bond, signify a double bond;

or the two bonds characterised by wavy lines are absent in ring B and replaced by a total of 4 hydrogen atoms, and the two wavy lines in ring A each, together with the respective parallel bond, signify a double bond;

or both in ring A and in ring B all of the 4 wavy bonds are absent and are replaced by a total of 8 hydrogen atoms;

or a salt thereof, if at least one salt-forming group is present.

4. A compound of formula I according to claim 1, with the designation 1,2,3,4-tetrahydrostaurosporine, or a pharmaceutically acceptable salt thereof.

5. A compound of formula I according to claim 1, selected from
8,9,10,11-Tetrahydrostaurosporine;
N-[4-(4-methylpiperaziN-1-ylmethyl)benzoyl]-1,2,3,4-tetrahydrostaurosporine;
N-(4-chloromethylbenzoyl)-1,2,3,4-tetrahydrostaurosporine;
N-(4-(pyrrolidin-1-ylmethyl)benzoyl)-1,2,3,4-tetrahydrostaurosporine;
N-(4-(morpholin-4-ylmethyl)benzoyl)-1,2,3,4-tetrahydrostaurosporine;
N-(4-(piperazin-1-ylmethyl)benzoyl)-1,2,3,4-tetrahydrostaurosporine;
N-ethyl-1,2,3,4-tetrahydrostaurosporine;
N-tosyl-1,2,3,4-tetrahydrostaurosporine;
N-triflouroacetyl-1,2,3,4-tetrahydrostaurosporine;
N-[4-(2-imidazol-1-yl-ethoxy)benzoyl]-1,2,3,4-tetrahydrostaurosporine;
N-methoxycarbonylmethyl-1,2,3,4-tetrahydrostaurosporine;
N-carboxymethyl-1,2,3,4-tetrahydrostaurosporine;
N-terephthaloylmethyl ester-1,2,3,4-tetrahydrostaurosporine;
N-terephthaloyl-1,2,3,4-tetrahydrostaurosporine;
N-(4-ethylpiperazinylcarbonylbenzoyl)-1,2,3,4-tetrahydrostaurosporine;
N-(2-cyanoethyl)-1,2,3,4-tetrahydrostaurosporine;
N-benzoyl-1,2,3,4-tetrahydrostaurosporine;
N,N-dimethyl -1,2,3,4-tetrahydrostaurosporinium iodide;
N-BOC-glycyl-1,2,3,4-tetrahydrostaurosporine;
N-glycyl-1,2,3,4-tetrahydrostaurosporine;
N-(3-(tert-butoxycarbonyl)propyl)-1,2,3,4-tetrahydrostaurosporine;
N-(3-carboxypropyl)-1,2,3,4-tetrahydrostaurosporine;
N-(4-imidazol-1-yl)benzoyl]-1,2,3,4-tetrahydrostaurosporine;
N-[(tetrahydro-2h-pyran-4-yloxy)acetyl]-1,2,3,4-tetrahydrostaurosporine;
N-BOC-l-alanyl-1,2,3,4-tetrahydrostaurosporine;
N-l-alanyl-1,2,3,4-tetrahydrostaurosporine hydrochloride;
N-methyl-1,2,3,4-tetrahydro-6-methylstaurosporine;
N-(4-carboxyphenylaminocarbonyl)-1,2,3,4-tetrahydrostaurosporine;
N-(4-ethylphenylaminocarbonyl)-1,2,3,4-tetrahydrostaurosporine;

N-(N-phenylaminocarbonyl)-1,2,3,4-tetrahydrostaurosporine;
N-(N-[2-(1-morpholino)ethyl]aminocarbonyl)-1,2,3,4-tetrahydrostaurosporine;
N-(N-[4-methoxyphenyl]aminocarbonyl)-1,2,3,4-tetrahydrostaurosporine;
1,2,3,4-tetrahydro-6-methylstaurosporine;
N-BOC-1,2,3,4-tetrahydrostaurosporine;
N-BOC-1,2,3,4-tetrahydro-6-methylstaurosporine;
N-BOC-1,2,3,4-tetrahydro-6-methyl-7-oxo-staurosporine;
1,2,3,4,8,9,10,11-octahydrostaurosporine;
or a pharmaceutically acceptable salt thereof, if at least one salt-forming group is present.

6. A compound of formula I, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 5 for use in a method for the treatment of the human or animal body.

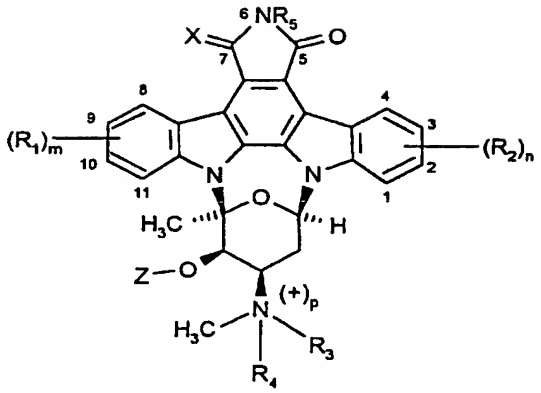
7. A pharmaceutical preparation, comprising a compound of formula I according to any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier.

8. Use of a compound of formula I, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 5 for the preparation of a pharmaceutical product for the treatment of a disease which responds to the inhibition of protein kinase C.

9. Use of a compound of formula I, or a pharmaceutically acceptable salt thereof, for the preparation of a pharmaceutical product for the treatment of a tumour disease.

10. Methods for the preparation of a compound of formula I characterised by the fact that

a) a compound of formula III,



(III)

wherein R_1, R_2, R_3, R_4, R_5, n, m, p, X and Z are as defined for compounds of formula I, or

b) for the preparation of a compound of formula I, wherein R_1, R_2, R_5, n, m, p, X, Z and wavy lines in rings A and B are as defined for a compound of formula I, R_3 and R_4 are independently of one another one of the radicals named under formula I subject to the proviso that at least one of the radicals is different from hydrogen, whereby R_4 may also be absent, reacting a compound of formula I, wherein R_3 is hydrogen and the meanings of the other symbols are as defined for a compound of formula I, with a compound of formula IV,

$$R_{3,4}\text{-}L \qquad (IV)$$

wherein $R_{3,4}$ has the meaning as defined for R_3 or R_4 under compounds of formula I, with the exception of hydrogen, and L stands for hydroxy or a nucleofugal leaving group, or

c) for the preparation of a compound of formula I, wherein R_1, R_2, R_5, n, m, p, X, Z and the wavy lines in rings A and B are as defined for compounds of formula I, R_4 is hydrogen or is absent, and R_3 is a radical of the subformula Y-C(=W)-, wherein W is oxygen or sulfur and Y is an amino group or a substituted amino group, carbamoylating a compound of formula I, wherein R_3 is hydrogen, R_4 is hydrogen or is absent, and the meanings of the other symbols are as defined for a compound of formula I, with a compound of formula V,

$$Y\text{=}C(\text{=}W) \qquad (V)$$

wherein Y is an amino group or a substituted amino group and W is oxygen or sulfur, or

d) for the preparation of a compound of formula I, wherein R_1, R_2, R_5, n, m, p, X, Z and the wavy lines in rings A and B are as defined for compounds of formula I, R_3 is one of the radicals named under formula I with the exception of hydrogen and acyl, and R_4 is hydrogen or is absent, adding a compound of formula I, wherein R_3 is hydrogen, R_4 is hydrogen or is absent, and the meanings of the other symbols are as defined for a compound of formula I, to a compound of formula VI,

R_3^* (VI)

which corresponds to the radical R_3 that is to be introduced, but differs insofar as it contains a double bond instead of a hydrogen atom and the bond to the radical of the molecule in formula I, or

e) for the preparation of a compound of formula I, wherein R_1, R_2, n, m, p, X, Z and wavy lines in rings A and B are as defined for a compound of formula I, R_4 is absent or is hydrogen, and R_3 and R_5 are identical to radicals named under formula I, although R_3 is not selected from acyl or hydrogen and R_5 is not selected from hydrogen, reductively alkylating a compound of formula I, wherein R_3 and R_5 are each hydrogen and the other symbols have the last-named meanings, with an aldehyde or ketone of formula VII,

$R_{3,5}^{**}$ (VII)

which corresponds to the radicals R_3 and R_5 that are to be introduced, but differs insofar as it contains a carbonyl group instead of the bonding methylene or methylidene group,

and, if so desired, converting an obtainable compound of formula I to a different compound of formula I; converting an obtainable free compound of formula I into a corresponding salt; converting a corresponding salt of a compound of formula I into the free compound or another salt of the corresponding compound of formula I; and/or separating an isomeric mixture into the individual isomers;

in reaction variants a), b), c), d), and e) and the conversions in the starting compounds, free functional groups which should not take part in the reaction are present in protected form, if necessary, and any protecting groups are removed after the reaction; and educts may exist in free form or in salt form, if a salt-forming group is present.